DAC
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent No. 5,886,036
Issued: March 23, 1999
Applicant: Abbott Laboratories
Application: 08/882,071
Filed: March 20, 1997
For: RETROVIRAL PROTEASE INHIBITING COMPOUNDS
Docket No.: 4681.US.D36
Date: November 10, 2000

Certificate of Mailing Under 37 C.F.R. 1.8(a)
Express Mail No.: EL 384 167 875 US

I hereby certify that this paper (along with any materials referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below as Express Mail Post Office to Addressee Service under 37 CFR 1.10 addressed to:

Box Patent Extension
Assistant Commissioner for Patents
Washington, D.C. 20231

Date of Deposit: November 10, 2000

Kathleen T. Litz 11/10/2000
Kathleen T. Litz Date

TRANSMITTAL LETTER

Box Patent Extension
Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Enclosed herewith is a Patent Term Extension Application For U.S. Patent No. 5,886,036 Pursuant to 35 U.S.C. §156 (in duplicate) of Abbott Laboratories in the above-identified patent application entitled RETROVIRAL PROTEASE INHIBITING COMPOUNDS.

Also enclosed are:
° True Copy of Applicant's Patent Term Extension Application For U.S. Patent No. 5,886,036 Pursuant To 35 U.S.C. §156
° Return-Receipt Postcard

The Commissioner is hereby authorized to charge any additional Filing Fees required under 37 CFR §1.16, as well as any patent application processing fees under 37 CFR §1.17 associated with this communication for which full payment has not been tendered, to Deposit Account NO. 01-0025. A duplicate copy of this sheet is enclosed.

Abbott Laboratories
D-377/AP6D-2
100 Abbott Park Road
Abbott Park, IL 60064-6050
Telephone: (847) 937-9516
Facsimile: (847) 938-2623

Respectfully submitted,
Abbott Laboratories

Dr. Steven R. Crowley
Registration No. 31,604
Agent for Applicant

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

U.S. Patent No. 5,886,036	**Certificate of Express Mailing**
	EL 384 167 875 US
Issued: March 23, 1999	I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 addressed to: Box Patent Extension Commissioner for Patents Washington, D.C. 20231 on the date indicated below:
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PATENT TERM EXTENSION APPLICATION
FOR U.S. PATENT No. 5,886,036 PURSUANT TO 35 U.S.C. §156

Box Patent Extension
Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Applicant hereby certifies that the attached is a true copy of Applicant's Patent Term Extension Application For U.S. Patent No. 5,886,036 Pursuant To 35 U.S.C. § 156 submitted on November 10, 2000.

Respectfully submitted,
Abbott Laboratories

Steven R Crowley

Dr. Steven R. Crowley
Registration No. 31,604
Agent for Applicant

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent No. 5,886,036

Issued: March 23, 1999

Applicant: Abbott Laboratories

Application: 08/882,071

Filed: March 20, 1997

For: RETROVIRAL PROTEASE INHIBITING COMPOUNDS

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Box Patent Extension
Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Enclosed herewith is a Patent Term Extension Application For U.S. Patent No. 5,886,036 Pursuant to 35 U.S.C. §156 (in duplicate) of Abbott Laboratories in the above-identified patent application entitled RETROVIRAL PROTEASE INHIBITING COMPOUNDS.

Also enclosed are:
° True Copy of Applicant's Patent Term Extension Application For U.S. Patent No. 5,886,036 Pursuant To 35 U.S.C. §156
° Return-Receipt Postcard

The Commissioner is hereby authorized to charge any additional Filing Fees required under 37 CFR §1.16, as well as any patent application processing fees under 37 CFR §1.17 associated with this communication for which full payment has not been tendered, to Deposit Account NO. 01-0025. A duplicate copy of this sheet is enclosed.

Abbott Laboratories
D-377/AP6D-2
100 Abbott Park Road
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Telephone: (847) 937-9516
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Respectfully submitted,
Abbott Laboratories

Dr. Steven R. Crowley
Registration No. 31,604
Agent for Applicant

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

U.S. Patent No. 5,886,036	**Certificate of Express Mailing**
Issued: March 23, 1999	**EL 384 167 875 US**
Applicant: Abbott Laboratories	I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 addressed to: Box Patent Extension Commissioner for Patents Washington, D.C. 20231 on the date indicated below:
Application: 08/882,071	
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Docket No.: 4681.US.D36	Date of Deposit: November 10, 2000
Date: November 10, 2000	Kathleen T. Litz 11/10/2000 Kathleen T. Litz Date

PATENT TERM EXTENSION APPLICATION
FOR U.S. PATENT No. 5,886,036 PURSUANT TO 35 U.S.C. §156

Box Patent Extension
Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

In accordance with 35 U.S.C. § 156 and 37 C.F.R. § 1.710 et seq., Applicant hereby applies to the Commissioner for an extension of the patent term for U.S. Patent No. 5,886,036, which covers and claims the recently approved drug product KALETRA (lopinavir/ritonavir) for the treatment of HIV infection. This application is submitted by the owner of record of the subject patent (Abbott Laboratories) through the patent attorneys/agents of Abbott Laboratories and fully complies with 35 U.S.C. § 156 and 37 C.F.R. § 1.710 et seq. which delineate the requirements for the application for extension of patent term.[1]

WRITTEN APPLICATION PURSUANT TO 37 C.F.R. § 1.740(a)

(1) Complete Identification of the Approved Product

The approved drug product that is the basis for this extension request is sold under the trademark KALETRA and has the generic name "lopinavir/ritonavir". KALETRA was approved for administration as an oral capsule formulation and for administration as an oral solution formulation. KALETRA is a co-formulation of lopinavir and ritonavir. It is claimed in U.S. Patent No. 5,886,036.

The chemical name for lopinavir is [1S-[1R*,(R*),3R*,4R*]]-N-[4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-alpha-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide.

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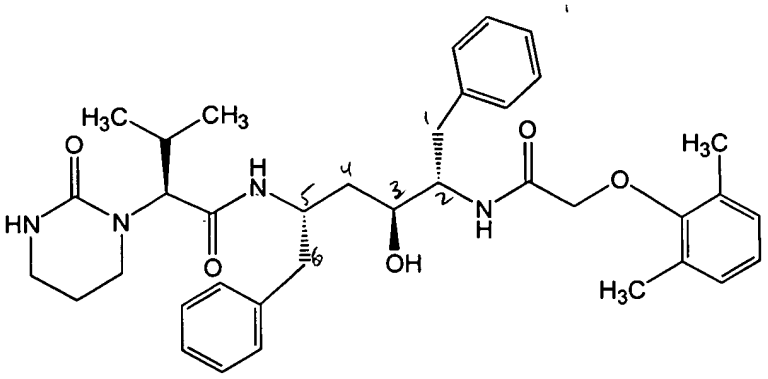
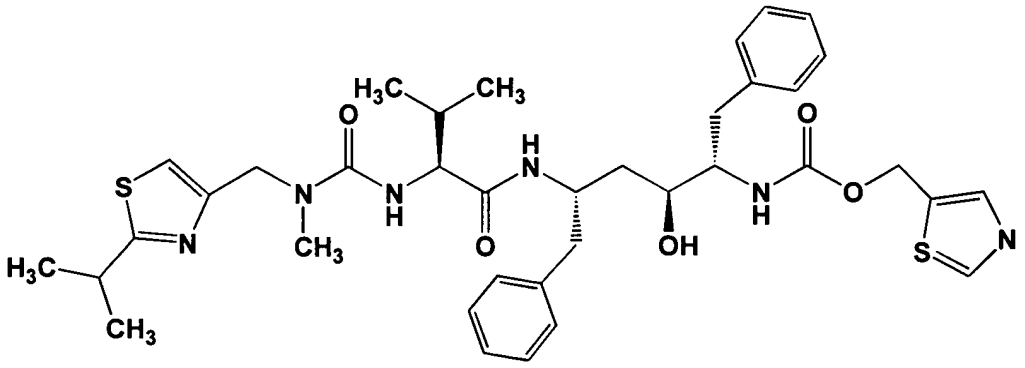
[1] The fact situation supporting this application for patent term extension is consistent with that described in fact pattern number 4 on page 1122 in *In re Alcon Laboratories Inc.*, 13 USPQ2d 1115.

The chemical structure of lopinavir is:



Lopinavir has the molecular formula $C_{37}H_{48}N_4O_5$ and a molecular weight of 628.80. Lopinavir is an inhibitor of the HIV protease. The remaining physical and chemical properties and descriptors are provided in the 8.5" X 11" paper copy of the package insert attached hereto at **Tab 1**.

The chemical name for ritonavir is (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane. An alternative chemical name for ritonavir is 10-hdyroxy-2-methyl-5—(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]. The chemical structure of ritonavir is:



Ritonavir has the molecular formula $C_{37}H_{48}N_6O_5S_2$ and a molecular weight of 720.95. Ritonavir, as co-formulated in KALETRA, inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

(2) Complete Identification of the Federal Statute

The Federal Statute under which the applicable regulatory review period occurred was 21 U.S.C. § 355, the provision which regulates the introduction of new drugs into commerce in the United States under the Federal Food, Drug and Cosmetic Act.

(3) Identification of the Date on Which the Product Received Permission for Commercial Marketing or Use

The date that marketing approval was given for the above-identified drug product pursuant to 21 U.S.C. § 355 was September 15, 2000 as shown in the copy of the Approval Letter attached hereto at **Tab 2**.

(4) Identification of Each Active Ingredient in the Drug Product

Applicant hereby asserts that the active ingredient lopinavir, as identified above, has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

Applicant hereby asserts that ritonavir, as identified above, has been previously approved under the Federal Food, Drug and Cosmetic Act pursuant to 21 U.S.C. § 355 on March 1, 1996 for commercial marketing or use under the trademark NORVIR as an inhibitor of HIV protease (but not as an inhibitor of CYP3A) for use in combination with nucleoside analogs or as monotherapy for the treatment of HIV infection.

(5) Statement That the Application is Being Submitted Within the Sixty Day Period

Applicant states and asserts that this application for patent term extension is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f). The product KALETRA first received permission for commercial marketing or use on **September 15, 2000**. Applicant must submit the patent term extension application within a 60 day period beginning on the date that the product first received permission for commercial marketing or use. Accordingly, the last day on which this application can be submitted **is November 13, 2000**.

(6) Identification of the Patent for Which an Extension is Sought

As stated above, the patent for which an extension is being sought is U.S. Patent No. 5,886,036 (the '036 patent) which issued on March 23, 1999 in the name of Kempf, et al. Pursuant to 35 U.S.C. § 154(c)(1), the '036 patent has an expiration date of twenty years from the earliest filing date, or **December 29, 2012**.

(7) Copy of Patent

A copy of U.S. Patent No. 5,886,036, including the entire specification and claims, is attached hereto at **Tab 3**. This patent does not contain drawings.

(8) Copy of Disclaimer, Certificate of Correction, Receipt of Maintenance Fee Payment or Reexamination Certificate

There have been no disclaimers, certificates of correction or reexaminations for the subject patent. In addition, the first maintenance fee is not due until 2002. Therefore, there are not yet any receipts for payment of maintenance fees.

(9) Statement That the Patent Claims the Approved Product With Showing

Applicant hereby asserts that U.S. Patent No. 5,886,036 claims the approved product. The listing of the patent claims that cover the approved product are as follows:

Claim 1 is directed to a combination pharmaceutical agent for the treatment of an HIV infection comprising (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane **(i.e., ritonavir)** or a pharmaceutically acceptable salt thereof and another HIV protease inhibiting compound.

Claim 1 covers KALETRA (lopinavir co-formulated with ritonavir), the approved drug product, when the other HIV protease inhibiting compound of Claim 1 is lopinavir.

Claim 8 is directed to a combination of pharmaceutical agents for the treatment of an HIV infection comprising (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane **(i.e., ritonavir)** or a pharmaceutically acceptable salt thereof and another HIV protease inhibiting compound.

Claim 8 covers KALETRA (lopinavir co-formulated with ritonavir), the approved drug product, when the other HIV protease inhibiting compound of Claim 8 is lopinavir.

Claim 15 is directed to (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane **(i.e., ritonavir)** or a pharmaceutically acceptable salt thereof and another HIV protease inhibitor for concomitant administration for the treatment of an HIV infection.

Claim 15 covers KALETRA (lopinavir co-formulated with ritonavir), the approved drug product, when the other HIV protease inhibitor of Claim 15 is lopinavir.

(10) Statement of Relevant Dates to Enable Determination of the Applicable Regulatory Review Period

The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

a) The investigational new drug (IND) numbers and the effective dates of the IND applications:

IND 51,715 (for oral capsules) effective **November 18, 1996**;

IND 55,984 (for oral solution) effective **June 6, 1998**;

b) The new drug application (NDA) numbers and the dates on which the new drug applications (NDA) were submitted:

NDA 21-226 (for oral capsules) submitted **June 1, 2000**;

NDA 21,251 (for oral solution) submitted **June 1, 2000**;

c) The date on which the both NDA's were approved:

September 15, 2000.

(11) A Brief Description of the Significant Activities Undertaken by Applicant

The significant activities undertaken by Abbott Laboratories during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities are described in the IND chronologies at **Tab 4** (oral capsule) and **Tab 5** (oral solution) and the NDA chronologies at **Tab 6** (oral capsule) and **Tab 7** (oral solution) attached hereto.

As evidenced by the summary of significant activities in the four regulatory chronologies, Applicant asserts that they pursued drug product approval for KALETRA (lopinavir/ritonavir) with due diligence throughout the regulatory review period.

(12) Statement Regarding Eligibility For Extension

Applicant asserts that U.S. Patent No. 5,886,036 covering the approved drug product KALETRA (lopinavir/ritonavir) is eligible for patent term extension.

Applicant hereby asserts that:

(a) U.S. Patent No. 5,886,036 has not expired before the filing of the application for extension;

(b) the term of the above-identified patent has never been extended;

(c) the application for extension is being submitted by the owner of record of the above-identified patent through its attorneys/agents;

(d) the approved drug product has been subject to a regulatory review period before its commercial marketing or use; and

(e) the permission for the commercial marketing or use of the approved product after the regulatory review period is the first such permitted commercial marketing or use of the product under the provision of law under which the regulatory period occurred.

Applicant respectfully submits that they are entitled to an extension of 324 days which was calculated as follows:

Pursuant to 35 U.S.C. § 156(c), the term of a patent eligible for extension under subsection (a) shall be extended by the time equal to the regulatory review period for the approved product which period occurs after the date the patent is issued, except that, according to 35 U.S.C. § 156(c)(2), the period of extension shall include only one-half of the time remaining in the periods described in § 156(g)(1)(B)(i). The term "regulatory review period" is defined in 35 U.S.C. § 156(g)(1)(B)(i) and (ii).

The regulatory review period for a new drug is thus the sum of:

(i) the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 became effective for the approved product and ending on the date an application was initially submitted for such drug product under section 351, 505 or 507, and

(ii) the period beginning on the date the application was initially submitted for the approved drug product under section 351, subsection (b) of 505, or section 507 and ending on the date such application was approved under such section.

A. For KALETRA (lopinavir/ritonavir) **oral capsules**, the regulatory review period is the sum of:

(i) **November 18, 1996** to **June 1, 2000** (1290 days) and

(ii) **June 1, 2000** to **September 15, 2000** (106 days).

However, under 35 U.S.C. § 156(c), the relevant regulatory review period calculation starts from the patent issue date. Because the subject patent issued on **March 23, 1999**, the relevant

regulatory review period begins on March 23, 1999 and is the sum of:

(i) **March 23, 1999** to **June 1, 2000** (436 days) and

(ii) **June 1, 2000** to **September 15, 2000** (106 days).

In addition, 35 U.S.C. § 156(c)(2) requires that after the relevant regulatory review period is reduced for lack of diligence, "the period of extension shall include only one-half of the time remaining in the periods described in paragraphs (1)(B)(i) . . . ." In this case, Applicant asserts that the relevant regulatory review period should not be reduced for lack of diligence. Accordingly, the IND period of 436 days (taking into account the patent issue date) is reduced by half to **218 days**. The NDA period is similarly not affected by any lack of diligence and is also not affected by the issue date of the subject patent. Therefore, the Revised Regulatory Review Period is calculated as follows:

218 days + 106 days = **324 days**.

35 U.S.C. § 156(c)(3) further provides that if the period remaining in the term of the patent after the date of the approval of the product, when added to the revised regulatory review period, exceeds fourteen years, the period of extension shall be reduced so that the total of both such periods does not exceed fourteen years. In addition, according to 35 U.S.C. § 156(g)(6)(A), the period of extension determined on the basis of the regulatory review period may not exceed five years.

It is evident that the reduction pursuant to 35 U.S.C. § 156(c)(3) is not applicable because the total of the remaining term of the patent after the date of approval (12 years plus 105 days) when added to the revised regulatory review period (324 days) does not exceed fourteen years.

The term of the patent remaining after **September 15, 2000** (the NDA approval date) is calculated as follows:

Patent expiration date = **December 29, 2012** (twenty years from the earliest filing date).

September 15, 2000 to December 29, 2012 = **12 years plus 105 days**.

The extended period of the subject patent after approval if the entire Revised Regulatory Review Period is added to the patent term remaining after approval is calculated as follows:

12 years plus 105 days + 324 days = **13 years plus 64 days**.

It is also evident that the reduction pursuant to 35 U.S.C. § 156(g)(6)(A) is not applicable because Applicant's Revised Regulatory Review Period (324 days) does not reach the 5 year cap for the length of extension.

B. For KALETRA (lopinavir/ritonavir) **oral solution**, the regulatory review period is the sum of:

(iii) **June 6, 1998** to **June 1, 2000** (726 days) and

(iv) **June 1, 2000** to **September 15, 2000** (106 days).

However, under 35 U.S.C. § 156(c), the relevant regulatory review period calculation starts from the patent issue date. Because the subject patent issued on **March 23, 1999**, the relevant

regulatory review period begins on March 23, 1999 and is the sum of:

(iii) **March 23, 1999** to **June 1, 2000** (436 days) and

(iv) **June 1, 2000** to **September 15, 2000** (106 days).

In addition, 35 U.S.C. § 156(c)(2) requires that after the relevant regulatory review period is reduced for lack of diligence, "the period of extension shall include only one-half of the time remaining in the periods described in paragraphs (1)(B)(i) . . . ." In this case, Applicant asserts that the relevant regulatory review period should not be reduced for lack of diligence. Accordingly, the IND period of 436 days (taking into account the patent issue date) is reduced by half to **218 days**. The NDA period is similarly not affected by any lack of diligence and is also not affected by the issue date of the subject patent. Therefore, the Revised Regulatory Review Period is calculated as follows:

218 days + 106 days = **324 days**.

35 U.S.C. § 156(c)(3) further provides that if the period remaining in the term of the patent after the date of the approval of the product, when added to the revised regulatory review period, exceeds fourteen years, the period of extension shall be reduced so that the total of both such periods does not exceed fourteen years. In addition, according to 35 U.S.C. § 156(g)(6)(A), the period of extension determined on the basis of the regulatory review period may not exceed five years.

It is evident that the reduction pursuant to 35 U.S.C. § 156(c)(3) is not applicable because the total of the remaining term of the patent after the date of approval (12 years plus 105 days) when added to the revised regulatory review period (324 days) does not exceed fourteen years.

The term of the patent remaining after **September 15, 2000** (the NDA approval date) is calculated as follows:

Patent expiration date = **December 29, 2012** (twenty years from the earliest filing date).

September 15, 2000 to December 29, 2012 = **12 years plus 105 days**.

The extended period of the subject patent after approval if the entire Revised Regulatory Review Period is added to the patent term remaining after approval is calculated as follows:

12 years plus 105 days + 324 days = **13 years plus 64 days**.

It is also evident that the reduction pursuant to 35 U.S.C. § 156(g)(6)(A) is not applicable because Applicant's Revised Regulatory Review Period (324 days) does not reach the 5 year cap for the length of extension.

Net Patent Term Extension and Patent Term Expiration Date

Thus, because the Revised Regulatory Review Period is the same for both of the NDA approvals for the approved product, the Net Patent Term Extension is **324 days** and the Patent Expiration Date with extension is **November 18, 2013**.

(13) Duty to Disclose

Applicant hereby acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information that is material to the determination of entitlement to the extension sought.

(14) The Prescribed Fee for Acting on This Application

Applicant hereby authorizes withdrawal from Deposit Account No. 01-0025 the appropriate fee of $1,120.00 for receiving and acting on the application for extension pursuant to § 1.20(j)(1). Applicant also authorizes any additional fee as a result of any fee change to be withdrawn from the above deposit account.

(15) Name, Address and Telephone Number of Person to Whom Inquiries Should be Directed

The name, address and telephone number of the person to whom inquiries and correspondence relating to this application should be directed is the attorney listed below:

Steven F. Weinstock
Registration No. 30,117
Attorney for Applicant
ABBOTT LABORATORIES
D377/AP6D-2
100 Abbott Park Road
Abbott Park, Illinois 60064-6050
(847) 937-4555

(16) Certified Duplicate Copy of Application Papers

A certified duplicate of these application papers is provided herewith.

(17) Declaration Pursuant to 37 C.F.R. § 1.740(17)(b)

With respect to the application presented herewith for the extension of the term of U.S. Patent No. 5,886,036, Applicant hereby declares that the person signing below and making this declaration is:

(1) A patent agent authorized to practice before the U.S. Patent and Trademark Office and has general authority to act on behalf of the patent owner in patent matters in connection with U.S. Patent No. 5,886,036;

(2) the undersigned agent and Declarant has reviewed and understands the contents of this application for patent extension of U.S. Patent No. 5,886,036 being submitted pursuant to 37 C.F.R. § 1.740;

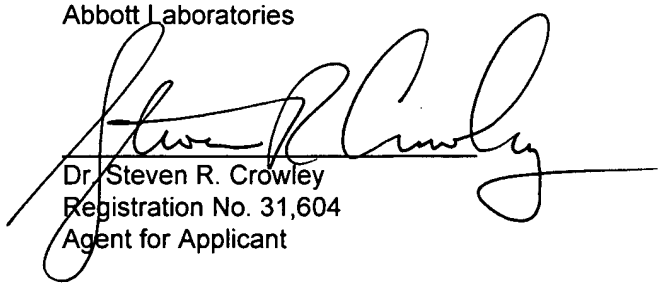
(3) the undersigned agent and Declarant believes the patent is subject to extension pursuant to § 1.710;

(4) the undersigned agent and Declarant believes an extension of the length claimed is justified under 35 U.S.C. § 156 and the applicable regulations; and

(5) the undersigned agent and Declarant believes the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in § 1.720.

I hereby declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true; that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 or Title 18 of the United States Code; and that such willful false statements may jeopardize the validity of this application.

Respectfully submitted,
Abbott Laboratories



Dr. Steven R. Crowley
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Agent for Applicant

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(847) 937-9516

(Nos. 3956 and 3959)
NEW

KALETRA™

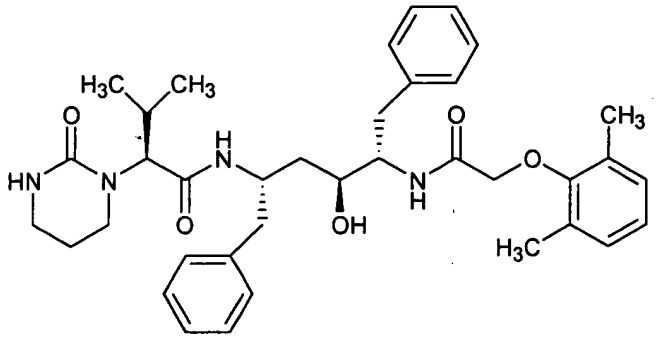
(lopinavir/ritonavir) capsules
(lopinavir/ritonavir) oral solution

R_x only

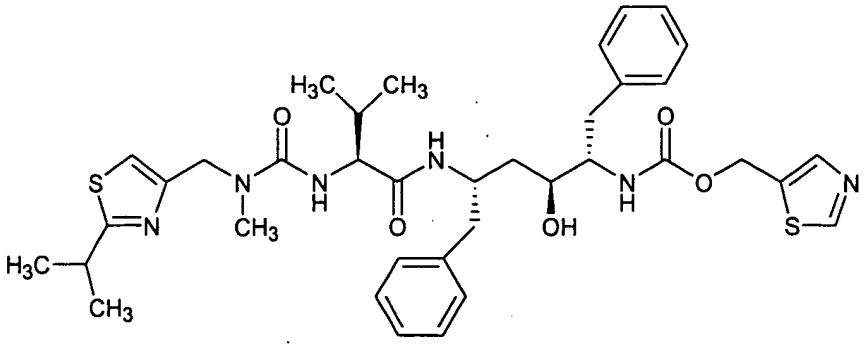
DESCRIPTION

KALETRA (lopinavir/ritonavir) is a co-formulation of lopinavir and ritonavir. Lopinavir is an inhibitor of the HIV protease. As co-formulated in KALETRA, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

Lopinavir is chemically designated as [1S-[1R*,(R*), 3R*, 4R*]]-N-[4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-alpha-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide. Its molecular formula is $C_{37}H_{48}N_4O_5$, and its molecular weight is 628.80. Lopinavir has the following structural formula:



Ritonavir is chemically designated as 10-Hydroxy-2-methyl-5-(1-methylethyl)-1- [2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]. Its molecular formula is $C_{37}H_{48}N_6O_5S_2$, and its molecular weight is 720.95. Ritonavir has the following structural formula:



Lopinavir is a white to light tan powder. It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water.

KALETRA capsules are available for oral administration in a strength of 133.3 mg lopinavir and 33.3 mg ritonavir with the following inactive ingredients: FD&C Yellow No. 6, gelatin, glycerin, oleic acid, polyoxyl 35 castor oil, propylene glycol, sorbitol special, titanium dioxide, and water.

KALETRA oral solution is available for oral administration as 80 mg lopinavir and 20 mg ritonavir per milliliter with the following inactive ingredients: Acesulfame potassium, alcohol, artificial cotton candy flavor, citric acid, glycerin, high fructose corn syrup, Magnasweet-110 flavor, menthol, natural & artificial vanilla flavor, peppermint oil, polyoxyl 40 hydrogenated castor oil, povidone, propylene glycol, saccharin sodium, sodium chloride, sodium citrate, and water.

KALETRA oral solution contains 42.4% alcohol (v/v).

CLINICAL PHARMACOLOGY

Microbiology

Mechanism of action: Lopinavir, an inhibitor of the HIV protease, prevents cleavage of the Gag-Pol polyprotein, resulting in the production of immature, non-infectious viral particles.

Antiviral activity in vitro: The *in vitro* antiviral activity of lopinavir against laboratory HIV strains and clinical HIV isolates was evaluated in acutely infected lymphoblastic cell lines and peripheral blood lymphocytes, respectively. In the absence of human serum, the mean 50% effective concentration (EC_{50}) of lopinavir against five different HIV-1 laboratory strains ranged from 10-27 nM (0.006 – 0.017 μg/mL, 1 μg/mL = 1.6 μM) and ranged from 4-11 nM (0.003 – 0.007 μg/mL) against several HIV-1 clinical isolates (n=6). In the presence of 50% human serum, the mean EC_{50} of lopinavir against these five laboratory strains ranged from 65 – 289 nM (0.04 – 0.18 μg/mL), representing a 7- to 11-fold attenuation. Combination drug activity studies with lopinavir and other protease inhibitors or reverse transcriptase inhibitors have not been completed.

Resistance: HIV-1 isolates with reduced susceptibility to lopinavir have been selected *in vitro*. The presence of ritonavir does not appear to influence the selection of lopinavir-resistant viruses *in vitro*.

The selection of resistance to KALETRA in antiretroviral treatment naive patients has not yet been characterized. In Phase II studies of 227 antiretroviral treatment naive and protease inhibitor experienced patients, isolates from 4 of 23 patients with quantifiable (>400 copies/mL) viral RNA following treatment with KALETRA for 12 to 100 weeks displayed significantly reduced susceptibility to lopinavir compared to the corresponding baseline viral isolates. Three of these patients had previously received treatment with a single protease inhibitor (nelfinavir, indinavir, or saquinavir) and one patient had received treatment with multiple protease inhibitors (indinavir, saquinavir and ritonavir). All four of these patients had at least 4 mutations associated with protease inhibitor resistance immediately prior to KALETRA therapy. Following viral rebound, isolates from these patients all contained additional mutations, some of which are recognized to be associated with protease inhibitor resistance. However, there are insufficient data at this time to identify lopinavir-associated mutational patterns in isolates from patients on KALETRA therapy. The assessment of these mutational patterns is under study.

Cross-resistance - Preclinical Studies: Varying degrees of cross-resistance have been observed among protease inhibitors. Little information is available on the cross-resistance of viruses that developed decreased susceptibility to lopinavir during KALETRA therapy.

The *in vitro* activity of lopinavir against clinical isolates from patients previously treated with a single protease inhibitor was determined. Isolates that displayed >4-fold reduced susceptibility to nelfinavir (n=13) and saquinavir (n=4), displayed <4-fold reduced susceptibility to lopinavir. Isolates with >4-fold reduced susceptibility to indinavir (n=16) and ritonavir (n=3) displayed a mean of 5.7- and 8.3-fold reduced susceptibility to lopinavir, respectively. Isolates from patients previously treated with two or more protease inhibitors showed greater reductions in susceptibility to lopinavir, as described in the following paragraph.

Clinical Studies - Antiviral activity of KALETRA in patients with previous protease inhibitor therapy. The clinical relevance of reduced *in vitro* susceptibility to lopinavir has been examined by assessing the virologic response to KALETRA therapy, with respect to baseline viral genotype and phenotype, in 56 NNRTI-naive patients with HIV RNA >1000 copies/mL despite previous therapy with at least two protease inhibitors selected from nelfinavir, indinavir, saquinavir and ritonavir (Study 957). The EC_{50} of lopinavir against the 56 baseline viral isolates ranged from 0.5- to 96-fold higher than the EC_{50} against wild type HIV. Fifty-five percent of these baseline isolates displayed a >4-fold reduced susceptibility to lopinavir with a mean reduction in lopinavir susceptibility of 27.9-fold.

After 24 weeks of treatment with KALETRA, efavirenz and nucleoside reverse transcriptase inhibitors, plasma HIV RNA ≤400 copies/mL was observed in 93% (27/29) and 65% (15/23) of patients with <10-fold and ≥10-fold reduced susceptibility to lopinavir at baseline, respectively.

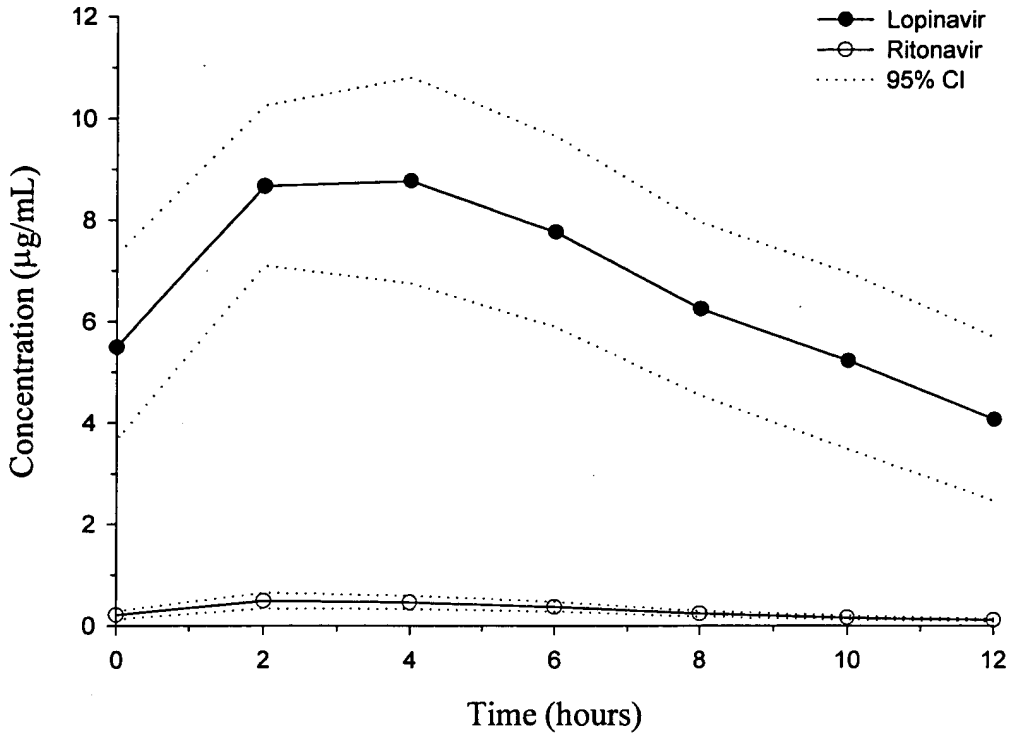
In addition, virologic response was observed in 96% (24/25) of patients whose baseline viral isolates contained up to 5 mutations recognized to be associated with protease inhibitor resistance. Fourteen of those 25 isolates contained mutations at positions 82, 84 and/or 90. Virologic response was observed in 67% (18/27) of patients whose baseline viral isolates contained 6 or more mutations, including those at positions 82, 84 and/or 90 plus multiple other mutations. There are insufficient data at this time to identify lopinavir-associated mutational patterns in isolates from patients on KALETRA therapy. Further studies are needed to assess the association between specific mutational patterns and virologic response rates.

Pharmacokinetics

The pharmacokinetic properties of lopinavir co-administered with ritonavir have been evaluated in healthy adult volunteers and in HIV-infected patients; no substantial differences were observed between the two groups. Lopinavir is essentially completely metabolized by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir. Across studies, administration of KALETRA 400/100 mg BID yields mean steady-state lopinavir plasma concentrations 15- to 20-fold higher than those of ritonavir in HIV-infected patients. The plasma levels of ritonavir are less than 7% of those obtained after the ritonavir dose of 600 mg BID. The *in vitro* antiviral EC_{50} of lopinavir is approximately 10-fold lower than that of ritonavir. Therefore, the antiviral activity of KALETRA is due to lopinavir.

Figure 1displays the mean steady-state plasma concentrations of lopinavir and ritonavir after KALETRA 400/100 mg BID for 3-4 weeks from a pharmacokinetic study in HIV-infected adult subjects (n=21).

Figure 1
Mean Steady-State Plasma Concentrations with 95% Confidence Intervals (CI) for HIV-Infected Adult Subjects (N = 21)



Absorption: In a pharmacokinetic study in HIV-positive subjects (n=21) without meal restrictions, multiple dosing with 400/100 mg KALETRA BID for 3 to 4 weeks produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 9.6 ± 4.4 µg/mL, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 5.5 ± 4.0 µg/mL. Lopinavir AUC over a 12 hour dosing interval averaged 82.8 ± 44.5 µg•h/mL. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established. Under nonfasting conditions (500 kcal, 25% from fat), lopinavir concentrations were similar following administration of KALETRA co-formulated capsules and liquid. When administered under fasting conditions, both the mean AUC and C_{max} of lopinavir were 22% lower for the KALETRA liquid relative to the capsule formulation.

Effects of Food on Oral Absorption: Administration of a single 400/100 mg dose of KALETRA capsules with a moderate fat meal (500-682 Kcal, 23 to 25% calories from fat) was associated with a mean increase of 48 and 23% in lopinavir AUC and C_{max}, respectively, relative to fasting. For KALETRA oral solution, the corresponding increases in lopinavir AUC and C_{max} were 80 and 54%, respectively. Relative to fasting, administration of KALETRA with a high fat meal (872 Kcal, 56% from fat) increased lopinavir AUC and C_{max} by 97 and 43%, respectively, for capsules, and 130 and 56%, respectively, for oral solution. To enhance bioavailability and minimize pharmacokinetic variability KALETRA should be taken with food.

Distribution: At steady state, lopinavir is approximately 98-99% bound to plasma proteins. Lopinavir binds to both alpha-1-acid glycoprotein (AAG) and albumin; however, it has a higher affinity for AAG. At steady state, lopinavir protein binding remains constant over the range of observed concentrations after 400/100 mg KALETRA BID, and is similar between healthy volunteers and HIV-positive patients.

Metabolism: *In vitro* experiments with human hepatic microsomes indicate that lopinavir primarily undergoes oxidative metabolism. Lopinavir is extensively metabolized by the hepatic cytochrome P450 system, almost exclusively by the CYP3A isozyme. Ritonavir is a potent CYP3A inhibitor which inhibits the metabolism of lopinavir, and therefore increases plasma levels of lopinavir. A ^{14}C-lopinavir study in humans showed that 89% of the plasma radioactivity after a single 400/100 mg KALETRA dose was due to parent drug. At least 13 lopinavir oxidative metabolites have been identified in man. Ritonavir has been shown to induce metabolic enzymes, resulting in the induction of its own metabolism. Pre-dose lopinavir concentrations decline with time during multiple dosing, stabilizing after approximately 10 to 16 days.

Elimination: Following a 400/100 mg ^{14}C-lopinavir/ritonavir dose, approximately 10.4 ± 2.3% and 82.6 ± 2.5% of an administered dose of ^{14}C-lopinavir can be accounted for in urine and feces, respectively, after 8 days. Unchanged lopinavir accounted for approximately 2.2 and 19.8% of the administered dose in urine and feces, respectively. After multiple dosing, less than 3% of the lopinavir dose is excreted unchanged in the urine. The half-life of lopinavir over a 12 hour dosing interval averaged 5-6 hours, and the apparent oral clearance (CL/F) of lopinavir is 6 to 7 L/h.

Special Populations:

Gender, Race and Age: Lopinavir pharmacokinetics have not been studied in elderly patients. No gender related pharmacokinetic differences have been observed in adult patients. No clinically important pharmacokinetic differences due to race have been identified.

Pediatric Patients: The pharmacokinetics of KALETRA 300/75 mg/m^2 BID and 230/57.5 mg/m^2 BID have been studied in a total of 53 pediatric patients, ranging in age from 6 months to 12 years. The 230/57.5 mg/m^2 BID regimen without nevirapine and the 300/75 mg/m^2 BID regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg BID regimen (without nevirapine).

The lopinavir mean steady-state AUC, C_{max}, and C_{min} were 72.6 ± 31.1 μg•h/mL, 8.2 ± 2.9 and 3.4 ± 2.1 μg/mL, respectively after KALETRA 230/57.5 mg/m^2 BID without nevirapine (n=12), and were 85.8 ± 36.9 μg•h/mL, 10.0 ± 3.3 and 3.6 ± 3.5

μg/mL, respectively after 300/75 mg/m^2 BID with nevirapine (n=12). The nevirapine regimen was 7 mg/kg BID (3 months to 8 years) or 4 mg/kg BID (>8 years).
Renal Insufficiency: Lopinavir pharmacokinetics have not been studied in patients with renal insufficiency; however, since the renal clearance of lopinavir is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency.
Hepatic Impairment: Lopinavir is principally metabolized and eliminated by the liver. Although KALETRA has not been studied in patients with hepatic impairment, lopinavir concentrations may be increased in these patients (see **PRECAUTIONS**).
Drug-Drug Interactions: See also **CONTRAINDICATIONS, WARNINGS** and **PRECAUTIONS: Drug Interactions**.

KALETRA is an inhibitor of the P450 isoform CYP3A *in vitro*. Co-administration of KALETRA and drugs primarily metabolized by CYP3A may result in increased plasma concentrations of the other drug, which could increase or prolong its therapeutic and adverse effects (see **CONTRAINDICATIONS**).

KALETRA inhibits CYP2D6 *in vitro*, but to a lesser extent than CYP3A. Clinically significant drug interactions with drugs metabolized by CYP2D6 are possible with KALETRA at the recommended dose, but the magnitude is not known. KALETRA does not inhibit CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations.

KALETRA has been shown *in vivo* to induce its own metabolism and to increase the biotransformation of some drugs metabolized by cytochrome P450 enzymes and by glucuronidation.

KALETRA is metabolized by CYP3A. Drugs that induce CYP3A activity would be expected to increase the clearance of lopinavir, resulting in lowered plasma concentrations of lopinavir. Although not noted with concurrent ketoconazole, co-administration of KALETRA and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

Drug interaction studies were performed with KALETRA and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of KALETRA on the AUC, C_{max} and C_{min} are summarized in Table 1 (effect of other drugs on lopinavir) and Table 2 (effect of KALETRA on other drugs). The effects of other drugs on ritonavir are not shown since they generally correlate with those observed with lopinavir (if lopinavir concentrations are decreased, ritonavir concentrations are decreased) unless otherwise indicated in the table footnotes. For information regarding clinical recommendations, see Table 6 in **PRECAUTIONS**.

Table 1: Drug Interactions: Pharmacokinetic Parameters for Lopinavir in the Presence of the Co-administered Drug
(See Precautions, Table 6 for Recommended Alterations in Dose or Regimen)

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of KALETRA (mg)	n	Ratio (with/without co-administered drug) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Amprenavir[1]	450 BID, 5 d 750 BID, 5 d	400/100 BID, 22 d	12 10	0.89 (0.83, 0.95)	0.85 (0.81, 0.90)	0.81 (0.74, 0.89)
Atorvastatin	20 QD, 4 d	400/100 BID, 14 d	12	0.90 (0.78, 1.06)	0.90 (0.79, 1.02)	0.92 (0.78, 1.10)
Efavirenz[2]	600 QHS, 9 d	400/100 BID, 9 d	11, 7*	0.97 (0.78, 1.22)	0.81 (0.64, 1.03)	0.61 (0.38, 0.97)
Ketoconazole	200 single dose	400/100 BID, 16 d	12	0.89 (0.80, 0.99)	0.87 (0.75, 1.00)	0.75 (0.55, 1.00)
Nevirapine	200 QD, 14 days; BID, 6 days	400/100 BID, 20 d	5, 9*	0.95 (0.73, 1.25)	0.99 (0.74, 1.32)	1.02 (0.68, 1.53)
	7 mg/kg or 4 mg/kg QD, 2 wk; BID 1 wk[3]	300/75 mg/m^2 BID, 3 wk	12, 15*	0.86 (0.64, 1.16)	0.78 (0.56, 1.09)	0.45 (0.25, 0.81)
Pravastatin	20 QD, 4 d	400/100 BID, 14 d	12	0.98 (0.89, 1.08)	0.95 (0.85, 1.05)	0.88 (0.77, 1.02)
Rifabutin	150 QD, 10 d	400/100 BID, 20 d	14	1.08 (0.97, 1.19)	1.17 (1.04, 1.31)	1.20 (0.96, 1.65)
Rifampin	600 QD, 10 d	400/100 BID, 20 d	22	0.45 (0.40, 0.51)	0.25 (0.21, 0.29)	0.01 (0.01, 0.02)
Ritonavir[4]	100 BID, 3-4 wk	400/100 BID, 3-4 wk	8, 21*	1.28 (0.94, 1.76)	1.46 (1.04, 2.06)	2.16 (1.29, 3.62)

All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated.

1 Composite effect of amprenavir 450 and 750 mg Q12h regimens on lopinavir pharmacokinetics.

2 The pharmacokinetics of ritonavir are unaffected by concurrent efavirenz.

3 Study conducted in HIV-positive pediatric subjects ranging in age from 6 months to 12 years.

4 Study conducted in HIV-positive adult subjects.

* Parallel group design; n for KALETRA + co-administered drug, n for KALETRA alone.

Table 2: Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of KALETRA
(See Precautions, Table 6 for Recommended Alterations in Dose or Regimen)

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of KALETRA (mg)	n	Ratio (with/without KALETRA) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Amprenavir	450 BID, 5 d 750 BID, 5 d	400/100 BID, 22 d	12 10	See text below for discussion of interaction.		
Atorvastatin	20 QD, 4 d	400/100 BID, 14 d	12	4.67 (3.35, 6.51)	5.88 (4.69, 7.37)	2.28 (1.91, 2.71)
Efavirenz	600 QHS, 9 d	400/100 BID, 9 d	11, 12*	0.91 (0.72, 1.15)	0.84 (0.62, 1.15)	0.84 (0.58, 1.20)
Ethinyl Estradiol	35 µg QD, 21 d (Ortho Novum®)	400/100 BID, 14 d	12	0.59 (0.52, 0.66)	0.58 (0.54, 0.62)	0.42 (0.36, 0.49)
Indinavir	600 single dose	400/100 BID, 10 d	11	See text below for discussion of interaction.		
Ketoconazole	200 single dose	400/100 BID, 16 d	12	1.13 (0.91, 1.40)	3.04 (2.44, 3.79)	N/A
Methadone	5 single dose	400/100 BID, 10 d	11	0.55 (0.48, 0.64)	0.47 (0.42, 0.53)	N/A
Nevirapine	200 QD, 14 d; BID, 6 d	400/100 BID, 20 d	5, 6*	1.05 (0.72, 1.52)	1.08 (0.72, 1.64)	1.15 (0.71, 1.86)
Norethindrone	1 QD, 21 d (Ortho Novum®)	400/100 BID, 14 d	12	0.84 (0.75, 0.94)	0.83 (0.73, 0.94)	0.68 (0.54, 0.85)
Pravastatin	20 QD, 4 d	400/100 BID, 14 d	12	1.26 (0.87, 1.83)	1.33 (0.91, 1.94)	N/A
Rifabutin 25-0-desacetyl rifabutin Rifabutin + 25-O-desacetyl rifabutin[1]	300 QD, 10 d; 150 QD, 10 d	400/100 BID, 10 d	12	2.12 (1.89, 2.38) 23.6 (13.7, 25.3) 3.46 (3.07, 3.91)	3.03 (2.79, 3.30) 47.5 (29.3, 51.8) 5.73 (5.08, 6.46)	4.90 (3.18, 5.76) 94.9 (74.0, 122) 9.53 (7.56, 12.01)
Saquinavir	800 single dose	400/100 BID, 10 d	11	See text below for discussion of interaction.		

All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated.
[1] Effect on the dose-normalized sum of rifabutin parent and 25-O-desacetyl rifabutin active metabolite.
* Parallel group design; n for KALETRA + co-administered drug, n for co-administered drug alone.
N/A =not available.

Effect of KALETRA on other Protease Inhibitors (PIs): The pharmacokinetics of single-dose indinavir and saquinavir, and multiple-dose amprenavir obtained in healthy subjects after at least 10 days of KALETRA 400/100 mg BID were compared to historical data in HIV-infected subjects (refer to Table 2 for information on study design and doses). Because of the limitations in the study design and the use of comparisons between healthy and HIV infected subjects, it is not possible to recommend definitive dosing recommendations. However, based on these comparisons, amprenavir 750 mg BID and indinavir 600 mg BID, when co-administered with KALETRA 400/100 mg BID, may produce a similar AUC, lower C_{max}, and higher C_{min} compared to their respective established clinical dosing regimens. Saquinavir 800 mg BID, when co-administered with KALETRA 400/100 mg BID, may produce a similar AUC and higher C_{min} to its respective established clinical dosing regimen (no comparative information regarding C_{max}). The clinical significance of the lower C_{max} and higher C_{min} is unknown. Appropriate doses of amprenavir, indinavir and saquinavir in combination with KALETRA with respect to safety and efficacy have not been established (see **PRECAUTIONS** – Table 6).

INDICATIONS AND USAGE

KALETRA is indicated in combination with other antiretroviral agents for the treatment of HIV-infection. This indication is based on analyses of plasma HIV RNA levels and CD4 cell counts in a controlled study of KALETRA of 24 weeks duration and in smaller uncontrolled dose-ranging studies of KALETRA of 72 weeks duration. At present, there are no results from controlled trials evaluating the effect of KALETRA on clinical progression of HIV.

Description of Clinical Studies

Patients Without Prior Antiretroviral Therapy

Study 863: KALETRA BID + stavudine + lamivudine compared to nelfinavir TID + stavudine + lamivudine

Study 863 is an ongoing, randomized, double-blind, multicenter trial comparing treatment with KALETRA (400/100 mg BID) plus stavudine and lamivudine versus nelfinavir (750 mg TID) plus stavudine and lamivudine in 653 antiretroviral treatment naive patients. Patients had a mean age of 38 years (range: 19 to 84), 57% were Caucasian, and 80% were male. Mean baseline CD4 cell count was 259 cells/mm^3 (range: 2 to 949 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.9 $\log_{10}$ copies/mL (range: 2.6 to 6.8 $\log_{10}$ copies/mL).

The percent of patients with HIV RNA <400 copies/mL and outcomes of patients through 24 weeks are summarized in Figure 2 and Table 3, respectively.

Figure 2: Virologic Response Through 24 Weeks (Study 863)

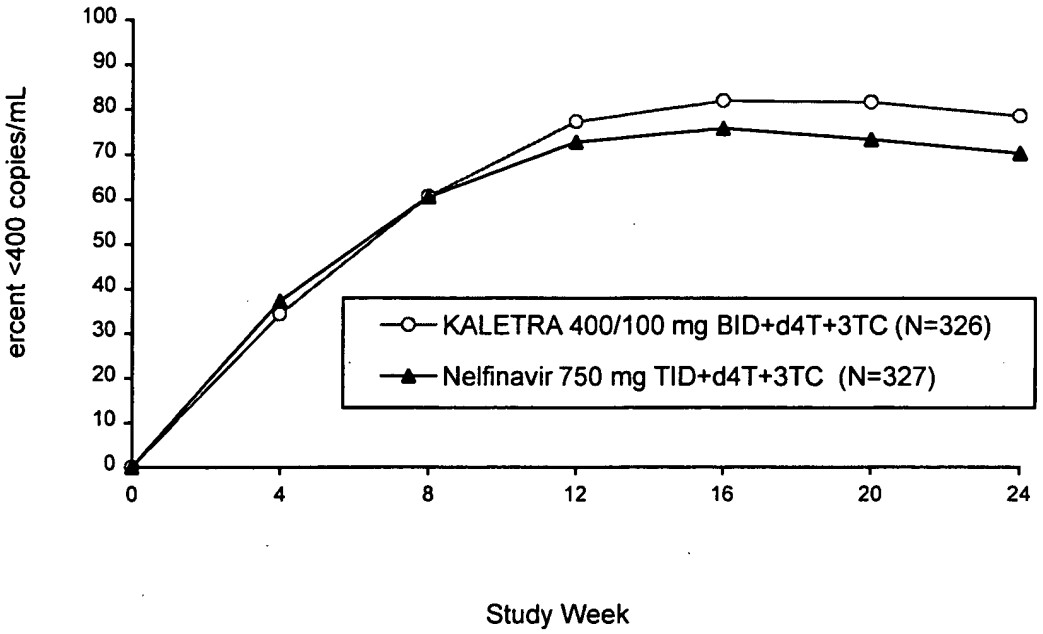


Table 3: Outcomes of Randomized Treatment Through Week 24 - (Study 863)

Outcome	KALETRA (400/100mg BID) + d4T + 3TC N=326	NELFINAVIR (750mg TID) + d4T + 3TC N=327
HIV RNA <400 copies/mL	79%	70%
HIV RNA >400 copies/mL	8%	16%
Discontinued due to KALETRA or nelfinavir adverse event*	2%	2%
Discontinued due to other adverse event*	2%	1%
Other**	8%	7%
Missing HIV RNA Level	2%	2%

*Includes laboratory abnormalities leading to discontinuation
**Lost to follow up, noncompliance, or consent withdrawn

In the KALETRA arm, the proportion <400 copies/mL for patients with baseline HIV RNA >100,000 copies/mL (78%) was similar to that for patients with baseline HIV RNA <100,000 copies/mL (81%).

Through 24 weeks of therapy, the proportion of patients with HIV RNA <50 copies/mL was 65% in the KALETRA arm and 60% in the nelfinavir arm.

Through 24 weeks of therapy, the mean increase from baseline in CD4 cell count was 154 cells/mm^3 for the KALETRA arm and 150 cells/mm^3 for the nelfinavir arm.

Four patients in the KALETRA arm and 6 patients in the nelfinavir arm experienced a new CDC Class C event following at least one week of treatment, including 3 patients in each arm who achieved HIV RNA <400 copies/mL at 24 weeks.

Study 720: KALETRA BID + stavudine + lamivudine

Study 720 is an ongoing, randomized, blinded, multicenter trial evaluating treatment with KALETRA at three dose levels (Group I: 200/100 mg BID and 400/100 mg BID; Group II: 400/100 mg BID and 400/200 mg BID) plus lamivudine (150 mg BID) and stavudine (40 mg BID) in 100 patients. All patients were converted to open-label KALETRA at the 400/100 mg BID dose between weeks 48 and 72 of the study. Patients had a mean age of 35 years (range: 21 to 59), 70% were Caucasian, and 96% were male. Mean baseline CD4 cell count was 338 cells/mm^3 (range: 3 to 918 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.9 log_{10} copies/mL (range: 3.3 to 6.3 log_{10} copies/mL).

Through 72 weeks of treatment, the proportion of patients with HIV RNA < 400 (<50) copies/mL was 80% (78%) and the mean increase from baseline in CD4 cell count was 256 cells/mm^3 for the 51 patients originally randomized to the 400/100 mg dose of KALETRA. At 72 weeks, 13 patients (13%) had discontinued the study for any reason. Four discontinuations (4%) were secondary to adverse events or laboratory abnormalities, and one of these discontinuations (1%) was attributed to a KALETRA adverse event.

Patients with Prior Antiretroviral Therapy

Study 765: KALETRA BID + nevirapine + NRTIs

Study 765 is an ongoing, randomized, blinded, multicenter trial evaluating treatment with KALETRA at two dose levels (400/100 mg BID and 400/200 mg BID) plus nevirapine (200 mg BID) and two NRTIs in 70 single protease inhibitor experienced, non-nucleoside reverse transcriptase inhibitor (NNRTI) naive patients. Patients had a mean age of 40 years (range 22-66), were 73% Caucasian, and were 90% male. Mean baseline CD4 cell count was 372 cells/mm^3 (range 72 to 807 cells/μL) and mean baseline plasma HIV-1 RNA was 4.0 log_{10} copies/mL (range 2.9 to 5.8 log_{10} copies/mL).

Through 72 weeks of treatment, the proportion of patients with HIV RNA < 400 (<50) copies/mL was 75% (58%) and the mean increase from baseline in CD4 cell count was 174 cells/mm^3 for the 36 patients receiving the 400/100 mg dose of KALETRA. At 72 weeks, 13 patients (19%) had discontinued the study for any reason. Six discontinuations (9%) were secondary to adverse events or laboratory abnormalities, and three of these discontinuations (4%) were attributed to KALETRA adverse events.

CONTRAINDICATIONS

KALETRA is contraindicated in patients with known hypersensitivity to any of its ingredients, including ritonavir.

Co-administration of KALETRA is contraindicated with drugs that are highly dependent on CYP3A or CYP2D6 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in Table 4.

Table 4: Drugs That Are Contraindicated With KALETRA

Drug Class	Drugs Within Class That Are Contraindicated With KALETRA
Antiarrhythmics	Flecainide, Propafenone
Antihistamines	Astemizole, Terfenadine
Ergot Derivatives	Dihydroergotamine, Ergonovine, Ergotamine, Methylergonovine
GI motility agent	Cisapride
Neuroleptic	Pimozide
Sedative/hypnotics	Midazolam, Triazolam

WARNINGS

ALERT: Find out about drugs that should not be taken with KALETRA. This statement is included on the product's bottle label.

Drug Interactions

KALETRA is an inhibitor of the P450 isoform CYP3A. Co-administration of KALETRA and drugs primarily metabolized by CYP3A or CYP2D6 may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects (see **Pharmacokinetics: Drug-Drug Interactions, CONTRAINDICATIONS – Table 4: Drugs That Are Contraindicated With KALETRA, PRECAUTIONS - Table 5: Drugs That Should Not Be Co-administered With KALETRA** and **Table 6: Established and Other Potentially Significant Drug Interactions**).

Particular caution should be used when prescribing sildenafil in patients receiving KALETRA. Co-administration of KALETRA with sildenafil is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse events including hypotension, syncope, visual changes and prolonged erection (see **PRECAUTIONS: Drug Interactions** and the complete prescribing information for sildenafil.)

Concomitant use of KALETRA with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including KALETRA, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (e.g., atorvastatin or cerivastatin). The risk of myopathy, including rhabdomyolysis may be increased when HIV protease inhibitors, including KALETRA, are used in combination with these drugs.

Concomitant use of KALETRA and St. John's wort (hypericum perforatum), or products containing St. John's wort, is not recommended. Co-administration of protease inhibitors, including KALETRA, with St. John's wort is expected to substantially decrease protease inhibitor concentrations and may result in sub-optimal levels of lopinavir and lead to loss of virologic response and possible resistance to lopinavir or to the class of protease inhibitors.

Pancreatitis

Pancreatitis has been observed in patients receiving KALETRA therapy, including those who developed marked triglyceride elevations. In some cases, fatalities have been observed. Although a causal relationship to KALETRA has not been established, marked triglyceride elevations is a risk factor for development of pancreatitis (see **PRECAUTIONS – Lipid Elevations**). Patients with advanced HIV disease may be at

increased risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk for recurrence during KALETRA therapy.

Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis should occur. Patients who exhibit these signs or symptoms should be evaluated and KALETRA and/or other antiretroviral therapy should be suspended as clinically appropriate.

Diabetes Mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

PRECAUTIONS

Hepatic Impairment and Toxicity

KALETRA is principally metabolized by the liver; therefore, caution should be exercised when administering this drug to patients with hepatic impairment, because lopinavir concentrations may be increased. Patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk for developing further transaminase elevations.

Resistance/Cross-resistance

Various degrees of cross-resistance among protease inhibitors have been observed. The effect of KALETRA therapy on the efficacy of subsequently administered protease inhibitors is under investigation (see **MICROBIOLOGY**).

Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship between protease inhibitor therapy and these events has not been established.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Lipid Elevations

Treatment with KALETRA has resulted in large increases in the concentration of total cholesterol and triglycerides (see **ADVERSE REACTIONS** – Table 8). Triglyceride and cholesterol testing should be performed prior to initiating KALETRA therapy and at

periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate. See **PRECAUTIONS Table 6: Established and Other Potentially Significant Drug Interactions** for additional information on potential drug interactions with KALETRA and HMG-CoA reductase inhibitors.

Information for Patients

A statement to patients and health care providers is included on the product's bottle label: **"ALERT: Find out about drugs that should NOT be taken with KALETRA."** A Patient Package Insert (PPI) for KALETRA is available for patient information.

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using KALETRA. Patients should be advised to take KALETRA and other concomitant antiretroviral therapy every day as prescribed. KALETRA must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting with their doctor. If a dose of KALETRA is missed patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped the patient should not double the next dose.

Patients should be informed that KALETRA is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of KALETRA are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with KALETRA can reduce the risk of transmitting HIV to others through sexual contact.

KALETRA may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort.

Patients taking didanosine should take didanosine one hour before or two hours after KALETRA.

Patients receiving sildenafil should be advised that they may be at an increased risk of sildenafil-associated adverse events including hypotension, visual changes, and sustained erection, and should promptly report any symptoms to their doctor.

Patients receiving estrogen-based hormonal contraceptives should be instructed that additional or alternate contraceptive measures should be used during therapy with KALETRA.

KALETRA should be taken with food to enhance absorption.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy including protease inhibitors and that the cause and long-term health effects of these conditions are not known at this time.

Drug Interactions

KALETRA is an inhibitor of CYP3A (cytochrome P450 3A) both *in vitro* and *in vivo*. Co-administration of KALETRA and drugs primarily metabolized by CYP3A (e.g., dihydropyridine calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants and sildenafil) may result in increased plasma concentrations of the other drugs that could increase or prolong their therapeutic and adverse effects (see **Table 6: Established and Other Potentially Significant Drug Interactions**). Agents that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the

most susceptible to large increases in AUC (>3-fold) when co-administered with KALETRA.

KALETRA inhibits CYP2D6 *in vitro*, but to a lesser extent than CYP3A. Clinically significant drug interactions with drugs metabolized by CYP2D6 are possible with KALETRA at the recommended dose, but the magnitude is not known. KALETRA does not inhibit CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations.

KALETRA has been shown *in vivo* to induce its own metabolism and to increase the biotransformation of some drugs metabolized by cytochrome P450 enzymes and by glucuronidation.

KALETRA is metabolized by CYP3A. Co-administration of KALETRA and drugs that induce CYP3A may decrease lopinavir plasma concentrations and reduce its therapeutic effect (see **Table 6: Established and Other Potentially Significant Drug Interactions**). Although not noted with concurrent ketoconazole, co-administration of KALETRA and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

Drugs that are contraindicated and not recommended for co-administration with KALETRA are included in **Table 5: Drugs That Should Not Be Co-administered With KALETRA**. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Table 5: Drugs That Should Not Be Co-administered With KALETRA

Drug Class: Drug Name	Clinical Comment
Antiarrhythmics: flecainide, propafenone	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as cardiac arrhythmias.
Antihistamines: astemizole, terfenadine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterial: rifampin	May lead to loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors or other co-administered antiretroviral agents.
Ergot Derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: pimozide	CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative/Hypnotics: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

Table 6: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction
(See CLINICAL PHARMACOLOGY for Magnitude of Interaction, Tables 1 and 2)

Concomitant Drug Class: Drug Name	Effect on Concentration of lopinavir or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitors: efavirenz*, nevirapine*	↓ Lopinavir	A dose increase of KALETRA to 533/133 mg (4 capsules or 6.5 mL) twice daily taken with food should be considered when used in combination with efavirenz or nevirapine in patients where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence) (see **DOSAGE AND ADMINISTRATION**). NOTE: Efavirenz and nevirapine induce the activity of CYP3A and thus have the potential to decrease plasma concentrations of other protease inhibitors when used in combination with KALETRA.
Non-nucleoside Reverse Transcriptase Inhibitor: delavirdine	↑ Lopinavir	Appropriate doses of the combination with respect to safety and efficacy have not been established.
Nucleoside Reverse Transcriptase Inhibitor: didanosine		It is recommended that didanosine be administered on an empty stomach; therefore, didanosine should be given one hour before or two hours after KALETRA (given with food).
HIV-Protease Inhibitors: amprenavir*, indinavir*, saquinavir*	↑ Amprenavir (Similar AUC, ↓ C_{max}, ↑ C_{min}) ↑ Indinavir (Similar AUC, ↓ C_{max}, ↑ C_{min}) ↑ Saquinavir (Similar AUC, ↑ C_{min})	Appropriate doses of the combination with respect to safety and efficacy have not been established (see **CLINICAL PHARMACOLOGY**: Table 2 and Effect of KALETRA on other Protease Inhibitors (PIs)).
HIV-Protease Inhibitor: ritonavir*	↑ Lopinavir	Appropriate doses of additional ritonavir in combination with KALETRA with respect to safety and efficacy have not been established.
Other Agents		
Antiarrhythmics: amiodarone, bepridil, lidocaine (systemic), and quinidine	↑ Antiarrhythmics	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when co-administered with KALETRA, if available.
Anticoagulant: warfarin		Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ Lopinavir	Use with caution. KALETRA may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly.
Anti-infective: clarithromycin	↑ Clarithromycin	For patients with renal impairment, the following dosage adjustments should be considered:

		• For patients with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. • For patients with CL_{CR} <30 mL/min the dose of clarithromycin should be decreased by 75%. No dose adjustment for patients with normal renal function is necessary.
Antifungals: ketoconazole*, itraconazole	↑ Ketoconazole ↑ Itraconazole	High doses of ketoconazole or itraconazole (>200 mg/day) are not recommended.
Antimycobacterial: rifabutin*	↑ Rifabutin and rifabutin metabolite	Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg/day is recommended (i.e., a maximum dose of 150 mg every other day or three times per week). Increased monitoring for adverse events is warranted in patients receiving the combination. Further dosage reduction of rifabutin may be necessary.
Antiparasitic: atovaquone	↓ Atovaquone	Clinical significance is unknown; however, increase in atovaquone doses may be needed.
Calcium Channel Blockers, Dihydropyridine: e.g., felodipine, nifedipine, nicardipine	↑ Dihydropyridine calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: Dexamethasone	↓ Lopinavir	Use with caution. KALETRA may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly.
Disulfiram/metronidazole		KALETRA oral solution contains alcohol, which can produce disulfiram-like reactions when co-administered with disulfiram or other drugs that produce this reaction (e.g., metronidazole).
Erectile Dysfunction Agent: sildenafil	↑ Sildenafil	Use with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events.
HMG-CoA Reductase Inhibitors: atorvastatin*, cerivastatin	↑ Atorvastatin ↑ Cerivastatin	Use lowest possible dose of atorvastatin or cerivastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with KALETRA.
Immunosuppresants: cyclosporine, tacrolimus, rapamycin	↑ Immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with KALETRA.
Narcotic Analgesic: Methadone*	↓ Methadone	Dosage of methadone may need to be increased when co-administered with KALETRA.
Oral Contraceptive: ethinyl estradiol*	↓ Ethinyl estradiol	Alternative or additional contraceptive measures should be used when estrogen-based oral contraceptives and KALETRA are co-administered.

* See **CLINICAL PHARMACOLGY** for Magnitude of Interaction, Tables 1 and 2

Other Drugs:

Drug interaction studies reveal no clinically significant interaction between KALETRA and pravastatin, stavudine or lamivudine.

Based on known metabolic profiles, clinically significant drug interactions are not expected between KALETRA and fluvastatin, dapsone, trimethoprim/sulfamethoxazole, azithromycin, erythromycin, or fluconazole.

Zidovudine and Abacavir: KALETRA induces glucuronidation; therefore, KALETRA has the potential to reduce zidovudine and abacavir plasma concentrations. The clinical significance of this potential interaction is unknown.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term carcinogenicity studies of KALETRA in animal systems have not been completed.

Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, at levels of 50, 100 or 200 mg/kg/day, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 4-fold for males that of the exposure in humans with the recommended therapeutic dose (400/100 mg KALETRA BID). There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 9-fold for the females that of the exposure in humans. In rats dosed at levels of 7, 15 or 30 mg/kg/day there were no carcinogenic effects. In this study, the exposure at the high dose was approximately 0.7-fold that of the exposure in humans with the 400/100 mg KALETRA BID regimen. Based on the exposures achieved in the animal studies, the significance of the observed effects is not known. However, neither lopinavir nor ritonavir was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Lopinavir in combination with ritonavir at a 2:1 ratio produced no effects on fertility in male and female rats at levels of 10/5, 30/15 or 100/50 mg/kg/day. Based on AUC measurements, the exposures in rats at the high doses were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose (400/100 mg BID).

Pregnancy

Pregnancy Category C: No treatment-related malformations were observed when lopinavir in combination with ritonavir was administered to pregnant rats or rabbits. Embryonic and fetal developmental toxicities (early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations and skeletal ossification delays) occurred in rats at a maternally toxic dosage (100/50 mg/kg/day). Based on AUC measurements, the drug exposures in rats at 100/50 mg/kg/day were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir for males and females that of the exposures in humans at the recommended therapeutic dose (400/100 mg BID). In a peri- and postnatal study in rats, a developmental toxicity (a decrease in survival in pups between birth and postnatal day 21) occurred at 40/20 mg/kg/day and greater.

No embryonic and fetal developmental toxicities were observed in rabbits at a maternally toxic dosage (80/40 mg/kg/day). Based on AUC measurements, the drug exposures in rabbits at 80/40 mg/kg/day were approximately 0.6-fold for lopinavir and 1.0-fold for ritonavir that of the exposures in humans at the recommended therapeutic dose (400/100 mg BID). There are, however, no adequate and well-controlled studies in pregnant women. KALETRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to KALETRA, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that lopinavir is secreted in milk. It is not known whether lopinavir is secreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed **not to breast-feed if they are receiving KALETRA.**

Geriatric Use

Clinical studies of KALETRA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, appropriate caution should be exercised in the administration and monitoring of KALETRA in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Pediatric Use

The safety and pharmacokinetic profiles of KALETRA in pediatric patients below the age of 6 months have not been established. In HIV-infected patients age 6 months to 12 years, the adverse event profile seen during a clinical trial was similar to that for adult patients. The evaluation of the antiviral activity of KALETRA in pediatric patients in clinical trials is ongoing.

Study 940 is an ongoing open-label, multicenter trial evaluating the pharmacokinetic profile, tolerability, safety and efficacy of KALETRA oral solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL in 100 antiretroviral naive (44%) and experienced (56%) pediatric patients. All patients were non-nucleoside reverse transcriptase inhibitor naive. Patients were randomized to either 230 mg lopinavir/57.5 mg ritonavir per m^2 or 300 mg lopinavir/75 mg ritonavir per m^2. Naive patients also received lamivudine and stavudine. Experienced patients received nevirapine plus up to two nucleoside reverse transcriptase inhibitors.

Safety, efficacy and pharmacokinetic profiles of the two dose regimens were assessed after three weeks of therapy in each patient. After analysis of these data, all patients were continued on the 300 mg lopinavir/75 mg ritonavir per m^2 dose. Patients had a mean age of 5 years (range 6 months to 12 years) with 14% less than 2 years. Mean baseline CD4 cell count was 838 cells/mm^3 and mean baseline plasma HIV-1 RNA was 4.7 $\log_{10}$ copies/mL.

Through 24 weeks of therapy, the proportion of patients with HIV RNA < 400 copies/mL was 82% for antiretroviral naive patients and 66% for antiretroviral experienced patients. The mean increase from baseline in CD4 cell count was 328

cells/mm^3 for antiretroviral naive and 335 cells/mm^3 for antiretroviral experienced patients treated through 24 weeks. At 24 weeks, one patient (1%) had prematurely discontinued the study. This discontinuation was secondary to an HIV-related event in an antiretroviral experienced patient that was not attributed to a KALETRA adverse event.

Dose selection for patients 6 months to 12 years of age was based on the following results. The 230/57.5 mg/m^2 BID regimen without nevirapine and the 300/75 mg/m^2 BID regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg BID regimen (without nevirapine).

ADVERSE REACTIONS

Adults:

Treatment-Emergent Adverse Events: KALETRA has been studied in 612 patients as combination therapy in Phase I/II and Phase III clinical trials. The most common adverse event associated with KALETRA therapy was diarrhea, which was generally of mild to moderate severity. Rates of discontinuation of randomized therapy due to adverse events were 2.8% in KALETRA and 3.1% in nelfinavir treated patients in Study 863.

Drug related clinical adverse events of moderate or severe intensity in $\geq$ 2% of patients treated with combination therapy including KALETRA for up to 24 weeks (Phase III) and for up to 72 weeks (Phase I/II) are presented in Table 7. For other information regarding observed or potentially serious adverse events, please see **WARNINGS** and **PRECAUTIONS**.

Table 7: Percentage of Patients with Treatment-Emergent[1] Adverse Events of Moderate or Severe Intensity Reported in $\geq$ 2% of Adult Patients

	Antiretroviral Naive Patients			Protease Inhibitor Experienced Patients
	Study 863 (24 Weeks)		Study 720 (72 Weeks)	Phase I/II and Phase III
	KALETRA 400/100 mg TID + d4T + 3TC (N=326)	Nelfinavir 750 mg TID + d4T + 3TC (N=327)	KALETRA BID[2] + d4T + 3TC (N= 84)	KALETRA BID[3] + nevirapine + NRTIs (N= 186)
Body as a Whole				
Abdominal Pain	3.1%	2.4%	4.8%	1.1%
Asthenia	3.4%	2.8%	7.1%	5.4%
Headache	2.5%	1.8%	7.1%	1.6%
Pain	0.3%	0.0%	2.4%	1.6%
Digestive System				
Abnormal Stools	0.0%	0.3%	6.0%	1.6%
Diarrhea	13.8%	14.4%	23.8%	15.1%
Nausea	6.4%	4.0%	15.5%	2.2%
Vomiting	2.1%	2.4%	4.8%	1.6%
Nervous System				
Insomnia	1.5%	1.2%	2.4%	1.1%
Skin and Appendages				
Rash	0.6%	1.2%	3.6%	2.0%

[1] Includes adverse events of possible, probable or unknown relationship to study drug.

[2] Includes adverse event data from dose group I (400/100 mg BID only [N=16]) and dose group II (400/100 mg BID [N=35]) and 400/200 mg BID [N=36]). Within dosing groups, moderate to severe nausea of probable/possible relationship to KALETRA occurred at a higher rate in the 400/200 mg dose arm compared to the 400/100 mg dose arm in group II.

[3] Includes adverse event data from patients receiving 400/100 mg BID, 400/200 mg BID, and 533/133 mg BID for 16-72 weeks. All 186 patients received KALETRA in combination with NRTIs and either nevirapine or efavirenz.

Treatment-emergent adverse events occurring in less than 2% of adult patients receiving KALETRA in all phase II/III clinical trials and considered at least possibly related or of unknown relationship to treatment with KALETRA and of at least moderate intensity are listed below by body system.

Body as a Whole: Back pain, chest pain, chest pain substernal, chills, drug interaction, drug level increased, face edema, fever, flu syndrome, malaise, and viral infection.

Cardiovascular System: Deep vein thrombosis, hypertension, palpitation, thrombophlebitis, and vasculitis.

Digestive System: Anorexia, cholecystitis, constipation, dry mouth, dyspepsia, dysphagia, enterocolitis, eructation, esophagitis, fecal incontinence, flatulence, gastritis, gastroenteritis, gastrointestinal disorder, hemorrhagic colitis, increased appetite, pancreatitis, sialadenitis, stomatitis, and ulcerative stomatitis.

Endocrine System: Cushing's syndrome and hypothyroidism.

Hemic and Lymphatic System: Anemia, leukopenia, and lymphadenopathy.

Metabolic and Nutritional Disorders: Avitaminosis, dehydration, edema, glucose tolerance decreased, lactic acidosis, obesity, peripheral edema, and weight loss.

Musculoskeletal System: Arthralgia, arthrosis and myalgia.

Nervous System: Abnormal dreams, agitation, amnesia, anxiety, ataxia, confusion, depression, dizziness, dyskinesia, emotional lability, encephalopathy, hypertonia, libido decreased, nervousness, neuropathy, paresthesia, peripheral neuritis, somnolence, thinking abnormal, and tremor.

Respiratory System: Bronchitis, dyspnea, lung edema, and sinusitis.

Skin and Appendages: Acne, alopecia, dry skin, exfoliative dermatitis, furunculosis, maculopapular rash, nail disorder, pruritis, skin benign neoplasm, skin discoloration, and sweating.

Special Senses: Abnormal vision, eye disorder, otitis media, taste perversion, and tinnitus.

Urogenital System: Abnormal ejaculation, gynecomastia, hypogonadism male, kidney calculus, and urine abnormality.

Laboratory Abnormalities: The percentages of adult patients treated with combination therapy including KALETRA with Grade 3-4 laboratory abnormalities are presented in Table 8.

Table 8: Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% of Adult Patients

Variable	Limit[1]	Antiretroviral Naive Patients			Antiretroviral Experienced Patients
		Study 863 (24 Weeks)		Study 720 (72 Weeks)	Phase I/II and Phase III
		KALETRA 400/100 mg BID + d4T + 3TC (N=326)	Nelfinavir 750 mg TID + d4T + 3TC (N=327)	KALETRA BID[2] + d4T + 3TC (N=84)	KALETRA BID[3] + NNRTI + NRTIs (N=186)
Chemistry	High				
Glucose	>250 mg/dL	1.6%	0.6%	2.4%	4.4%
Uric Acid	>12 mg/dL	1.3%	0.3%	3.6%	0.5%
SGOT/AST	>180 U/L	0.3%	2.2%	9.5%	4.4%
SGPT/ALT	>215 U/L	1.0%	2.2%	8.3%	6.6%
GGT	>300 U/L	N/A	N/A	3.6%	24.6%[4]
Total Cholesterol	>300 mg/dL	6.7%	2.8%	14.3%	25.7%
Triglycerides	>750 mg/dL	5.1%	0.9%	10.7%	26.2%
Amylase	>2 x ULN	1.9%	1.9%	4.8%	3.3%

Chemistry	Low				
Inorganic Phosphorus	<1.5 mg/dL	0.0%	0.0%	0.0%	2.2%
Hematology	Low				
Neutrophils	0.75 x 10^9/L	0.6%	1.6%	2.4%	2.7%

[1] ULN = upper limit of the normal range; N/A = Not Applicable.
[2] Includes clinical laboratory data from dose group I (400/100 mg BID only [N=16]) and dose group II (400/100 mg BID [N=35] and 400/200 mg BID [N=36]).
[3] Includes clinical laboratory data from patients receiving 400/100 mg BID, 400/200 mg BID, and 533/133 mg BID for 16-72 weeks. All 186 patients received KALETRA in combination with NRTIs and either nevirapine or efavirenz.
[4] GGT was only measured in 69 patients receiving 400/100 mg BID or 400/200 mg BID in combination with nevirapine.

Pediatrics:

Treatment-Emergent Adverse Events: KALETRA has been studied in 100 pediatric patients 6 months to 12 years of age. The adverse event profile seen during a clinical trial was similar to that for adult patients.

Rash (2%) was the only drug-related clinical adverse event of moderate or severe intensity in ≥ 2% of pediatric patients treated with combination therapy including KALETRA (300/75 mg/m^2) for up to 24 weeks (Study 940). This includes adverse events of at least possible, probable or unknown relationship to study drug.

Laboratory Abnormalities: The percentages of pediatric patients treated with combination therapy including KALETRA with Grade 3-4 laboratory abnormalities are presented in Table 9.

Table 9: Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% Pediatric Patients

Variable	Limit[1]	KALETRA BID[2]+ RTIs (N=100)
Chemistry	High	
Total bilirubin	> 2.9 x ULN	3.0%
SGOT/AST	> 180 U/L	7.0%
SGPT/ALT	>215 U/L	4.0%
Total cholesterol	> 300 mg/dL	2.0%
Amylase	> 2.5 x ULN	4.0%
Chemistry	Low	
Sodium	< 130 mEq/L	3.0%
Hematology	Low	
Platelet Count	< 50 x 10^9/L	4.0%
Neutrophils	< 0.40 x 10^9/L	2.0%

[1] ULN = upper limit of the normal range.
[2] Includes clinical laboratory data from the 230/57.5 mg per m^2 (N=49) and 300/75 mg per m^2 (N=51) dose arms.

OVERDOSAGE

KALETRA oral solution contains 42.4% alcohol (v/v). Accidental ingestion of the product by a young child could result in significant alcohol-related toxicity and could approach the potential lethal dose of alcohol.

Human experience of acute overdosage with KALETRA is limited. Treatment of overdose with KALETRA should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with KALETRA. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug. Since KALETRA is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the drug.

DOSAGE AND ADMINISTRATION

Adults

The recommended dosage of KALETRA is 400/100 mg (3 capsules or 5.0 mL) twice daily taken with food.

Concomitant therapy: Efavirenz or nevirapine: A dose increase of KALETRA to 533/133 mg (4 capsules or 6.5 mL) twice daily taken with food should be considered when used in combination with efavirenz or nevirapine in treatment experienced patients where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence) (see **CLINICAL PHARMACOLOGY – Drug Interactions** and/or **PRECAUTIONS** – Table 6).

Pediatric Patients

In children 6 months to 12 years of age, the recommended dosage of KALETRA oral solution is 12/3 mg/kg for those 7 to <15 kg and 10/2.5 mg/kg for those 15 to 40 kg (approximately equivalent to 230/57.5 mg/m^2) twice daily taken with food, up to a maximum dose of 400/100 mg in children >40 kg (5.0 mL or 3 capsules) twice daily. The following table contains dosing guidelines for KALETRA oral solution based on body weight.

Weight (kg)	Dose (mg/kg)*	Volume of oral solution BID (80 mg lopinavir/20 mg ritonavir per mL)
Without nevirapine or efavirenz		
7 to <15kg	12 mg/kg BID	
7 to 10 kg		1.25 mL
>10 to <15 kg		1.75 mL
15 to 40 kg	10 mg/kg BID	
15 to 20 kg		2.25 mL
>20 to 25 kg		2.5 mL
>25 to 30 kg		3.0 mL
>30 to 40 kg		3.5 mL
>40 kg	Adult dose	5 mL (or 3 capsules)

* Dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg/20 mg per mL).
Note: Use adult dosage recommendation for children >12 years of age.

Concomitant therapy: Efavirenz or nevirapine: A dose increase of KALETRA oral solution to 13/3.25 mg/kg for those 7 to <15 kg and 11/2.75 mg/kg for those 15 to 50 kg (approximately equivalent to 300/75 mg/m^2) twice daily taken with food, up to a maximum dose of 533/133 mg in children >50 kg twice daily should be considered when used in combination with efavirenz or nevirapine in treatment experienced children 6 months to 12 years of age in which reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). The following table contains dosing guidelines for KALETRA oral solution based on body weight, when used in combination with efavirenz or nevirapine in children (see **CLINICAL PHARMACOLOGY – Drug Interactions** and/or **PRECAUTIONS** – Table 6).

Weight (kg)	Dose (mg/kg)*	Volume of oral solution BID (80 mg lopinavir/20 mg ritonavir per mL)

With nevirapine or efavirenz		
7 to <15 kg	13 mg/kg BID	
7 to 10 kg		1.5 mL
>10 to <15 kg		2.0 mL
15 to 50 kg	11 mg/kg BID	
15 to 20 kg		2.5 mL
>20 to 25 kg		3.25 mL
>25 to 30 kg		4.0 mL
>30 to 40 kg		4.5 mL
>40 to 50 kg		5.0 mL (or 3 capsules)
>50 kg	Adult dose	6.5 mL (or 4 capsules)

* Dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg/20 mg per mL).
Note: Use adult dosage recommendation for children >12 years of age.

HOW SUPPLIED

KALETRA (lopinavir/ritonavir) capsules are orange soft gelatin capsules imprinted with the corporate logo and the Abbo-Code PK. KALETRA is available as 133.3 mg lopinavir/33.3 mg ritonavir capsules in the following package sizes:
Bottles of 180 capsules each..... (**NDC** 0074-3959-77)
Packages of 120 unit dose blisters.....(**NDC** 0074-3959-11)

Recommended storage: Store KALETRA soft gelatin capsules at 36°F - 46°F (2°C - 8°C) until dispensed. Avoid exposure to excessive heat. For patient use, refrigerated KALETRA capsules remain stable until the expiration date printed on the label. If stored at room temperature up to 77°F (25°C), capsules should be used within 2 months.

KALETRA (lopinavir/ritonavir) oral solution is a light yellow to orange colored liquid supplied in amber-colored multiple-dose bottles containing 400 mg lopinavir/100 mg ritonavir per 5 mL (80 mg lopinavir/20 mg ritonavir per mL) packaged with a marked dosing cup in the following size:
160 mL bottle.....(**NDC** 0074-3956-46)

Recommended storage: Store KALETRA oral solution at 36°F - 46°F (2°C - 8°C) until dispensed. Avoid exposure to excessive heat. For patient use, refrigerated KALETRA oral solution remains stable until the expiration date printed on the label. If stored at room temperature up to 77°F (25°C), oral solution should be used within 2 months.

Revised: NEW

ABBOTT
LABORATORIES
NORTH CHICAGO, IL 60064, U.S.A.
PRINTED IN U.S.A.

----------(Perforation)----------

KALETRA™
(lopinavir/ritonavir) capsules
(lopinavir/ritonavir) oral solution

ALERT: Find out about drugs that should NOT be taken with KALETRA. Please also read the section "MEDICINES YOU SHOULD NOT TAKE WITH KALETRA."

Patient Information

KALETRA™ (kuh-LEE-tra)

Generic Name: lopinavir/ritonavir (lop-IN-uh-veer/rit-ON-uh-veer)

Read this leaflet carefully before you start taking KALETRA. Also, read it each time you get your KALETRA prescription refilled, in case something has changed. This information does not take the place of talking with your doctor when you start this medicine and at check ups. Ask your doctor if you have any questions about KALETRA.

What is KALETRA and how does it work?

KALETRA is a combination of two medicines. They are lopinavir and ritonavir. KALETRA is a type of medicine called an HIV (human immunodeficiency virus) protease (PRO-tee-ase) inhibitor. KALETRA is always used in combination with other anti-HIV medicines to treat people with human immunodeficiency virus (HIV) infection. KALETRA is for adults and for children age 6 months and older.

HIV infection destroys CD4 (T) cells, which are important to the immune system. After a large number of T cells are destroyed, acquired immune deficiency syndrome (AIDS) develops.

KALETRA blocks HIV protease, a chemical which is needed for HIV to multiply. KALETRA reduces the amount of HIV in your blood and increases the number of T cells. Reducing the amount of HIV in the blood reduces the chance of death or infections that happen when your immune system is weak (opportunistic infections).

Does KALETRA cure HIV or AIDS?

KALETRA does not cure HIV infection or AIDS. The long-term effects of KALETRA are not known at this time. People taking KALETRA may still get opportunistic infections or other conditions that happen with HIV infection. Some of these conditions are pneumonia, herpes virus infections, and *Mycobacterium avium* complex (MAC) infections.

Does KALETRA reduce the risk of passing HIV to others?

KALETRA does not reduce the risk of passing HIV to others through sexual contact or blood contamination. Continue to practice safe sex and do not use or share dirty needles.

How should I take KALETRA?

- You should stay under a doctor's care when taking KALETRA. Do not change your treatment or stop treatment without first talking with your doctor.

- You must take KALETRA every day exactly as your doctor prescribed it. The dose of KALETRA may be different for you than for other patients. Follow the directions from your doctor, exactly as written on the label.

- Dosing in adults (including children 12 years of age and older):
  The usual dose for adults is 3 capsules (400/100 mg) or 5.0 mL of the oral solution twice a day (morning and night), in combination with other anti-HIV medicines.

- Dosing in children from 6 months to 12 years of age:
  Children from 6 months to 12 years of age can also take KALETRA. The child's doctor will decide the right dose based on the child's weight.

- Take KALETRA with food to help it work better.

- Do not change your dose or stop taking KALETRA without first talking with your doctor.

- When your KALETRA supply starts to run low, get more from your doctor or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to KALETRA and become harder to treat.

- Be sure to set up a schedule and follow it carefully.

- Only take medicine that has been prescribed specifically for you. Do not give KALETRA to others or take medicine prescribed for someone else.

What should I do if I miss a dose of KALETRA?

It is important that you do not miss any doses. If you miss a dose of KALETRA, take it as soon as possible and then take your next scheduled dose at its regular time. If it is almost time for your next dose, do not take the missed dose. Wait and take the next dose at the regular time. Do not double the next dose.

What happens if I take too much KALETRA?

If you suspect that you took more than the prescribed dose of this medicine, contact your local poison control center or emergency room immediately.

As with all prescription medicines, KALETRA should be kept out of the reach of young children. KALETRA liquid contains a large amount of alcohol. If a toddler or young child accidentally drinks more than the recommended dose of KALETRA, it could make him/her sick from too much alcohol. Contact your local poison control center or emergency room immediately if this happens.

Who should not take KALETRA?

Together with your doctor, you need to decide whether KALETRA is right for you.

- Do not take KALETRA if you are taking certain medicines. These could cause serious side effects that could cause death. Before you take KALETRA, you must tell your doctor about all the medicines you are taking or are planning to take. These include other prescription and non-prescription medicines and herbal supplements.

For more information about medicines you should not take with KALETRA, please read the section titled "MEDICINES YOU SHOULD NOT TAKE WITH KALETRA."

- Do not take KALETRA if you have an allergy to KALETRA or any of its ingredients, including ritonavir or lopinavir.

Can I take KALETRA with other medications?*

KALETRA may interact with other medicines, including those you take without a prescription. You must tell your doctor about all the medicines you are taking or planning to take before you take KALETRA.

MEDICINES YOU SHOULD NOT TAKE WITH KALETRA:

- Do not take the following medicines with KALETRA because they can cause serious problems or death if taken with KALETRA.

- Dihydroergotamine, ergonovine, ergotamine and methylergonovine such as Cafergot®, Migranal®, D.H.E. 45®, Ergotrate Maleate, Methergine, and others
- Halcion® (triazolam)
- Hismanal® (astemizole)
- Orap® (pimozide)
- Propulsid® (cisapride)
- Rhythmol® (propafenone)
- Seldane® (terfenadine)
- Tambocor® (flecainide)
- Versed® (midazolam)

- Do not take KALETRA with rifampin, also known as Rimactane®, Rifadin®, Rifater®, or Rifamate®. Rifampin may lower the amount of KALETRA in your blood and make it less effective.

- Do not take KALETRA with St. John's wort (hypericum perforatum), an herbal product sold as a dietary supplement or products containing St. John's wort. Talk with your doctor if you are taking or planning to take St. John's wort. Taking St. John's wort may decrease KALETRA levels and lead to increased viral load and possible resistance to KALETRA or cross-resistance to other anti-HIV medicines.

- Do not take KALETRA with the cholesterol-lowering medicines Mevacor® (lovastatin) or Zocor® (simvastatin) because of possible serious reactions. There is also an increased risk of drug interactions between KALETRA and Lipitor® (atorvastatin) and Baycol® (cerivastatin); talk to your doctor before you take any of these cholesterol-reducing medicines with KALETRA.

Medicines that require dosage adjustments:

It is possible that your doctor may need to increase or decrease the dose of other medicines when you are also taking KALETRA. Remember to tell your doctor all medicines you are taking or plan to take.

Before you take Viagra® (sildenafil) with KALETRA, talk to your doctor about problems these two medicines can cause when taken together. You may get increased side effects of VIAGRA, such as low blood pressure, vision changes, and penis erection lasting more than 4 hours. If an erection lasts longer than 4 hours, get medical help right away to avoid permanent damage to your penis. Your doctor can explain these symptoms to you.

- If you are taking oral contraceptives ("the pill") to prevent pregnancy, you should use an additional or different type of contraception since KALETRA may reduce the effectiveness of oral contraceptives.

- Efavirenz (Sustiva™) or nevirapine (Viramune®) may lower the amount of KALETRA in your blood. Your doctor may increase your dose of KALETRA if you are also taking efavirenz or nevirapine.

- If you are taking Mycobutin® (rifabutin), your doctor will lower the dose of Mycobutin.

- **A change in therapy should be considered if you are taking KALETRA with:**
  Phenobarbital
  Phenytoin (Dilantin® and others)
  Carbamazepine (Tegretol® and others)
  These medicines may lower the amount of KALETRA in your blood and make it less effective.

- **Other Special Considerations:**
  KALETRA oral solution contains alcohol. Talk with your doctor if you are taking or

planning to take metronidazole or disulfiram. Severe nausea and vomiting can occur.

- **If you are taking both didanosine (Videx®) and KALETRA:**
  Didanosine (Videx®) should be taken one hour before or two hours after KALETRA.

What are the possible side effects of KALETRA?

- This list of side effects is **not** complete. If you have questions about side effects, ask your doctor, nurse, or pharmacist. You should report any new or continuing symptoms to your doctor right away. Your doctor may be able to help you manage these side effects.

- The most commonly reported side effects of moderate severity that are thought to be drug related are: abnormal stools (bowel movements), diarrhea, feeling weak/tired, headache, and nausea. Children taking KALETRA may sometimes get a skin rash.

- Blood tests in patients taking KALETRA may show possible liver problems. People with liver disease such as Hepatitis B and Hepatitis C who take KALETRA may have worsening liver disease. Liver problems including death have occurred in patients taking KALETRA. In studies, it is unclear if KALETRA caused these liver problems because some patients had other illnesses or were taking other medicines.

- Some patients taking KALETRA can develop serious problems with their pancreas (pancreatitis), which may cause death. You have a higher chance of having pancreatitis if you have had it before. Tell your doctor if you have nausea, vomiting, or abdominal pain. These may be signs of pancreatitis.

- Some patients have large increases in triglycerides and cholesterol. The long-term chance of getting complications such as heart attacks or stroke due to increases in triglycerides and cholesterol caused by protease inhibitors is not known at this time.

- Diabetes and high blood sugar (hyperglycemia) occur in patients taking protease inhibitors such as KALETRA. Some patients had diabetes before starting protease inhibitors, others did not. Some patients need changes in their diabetes medicine. Others needed new diabetes medicine.

- Changes in body fat happen in some patients getting anti-HIV medicines. These changes may include increased fat in the upper back and neck ("buffalo hump"), breast and abdomen (stomach area). Loss of fat from the face, legs, and arms may also happen. The cause and long-term health effects of these conditions are not known at this time.

- Some patients with hemophilia have increased bleeding with protease inhibitors.

- There have been other side effects in patients taking KALETRA. However, these side effects may have been due to other medicines that patients were taking or to the

illness itself. Some of these side effects can be serious.

What should I tell my doctor before taking KALETRA?

- *If you are pregnant or planning to become pregnant:* The effects of KALETRA on pregnant women or their unborn babies are not known.

- *If you are breast-feeding:* You should not breast-feed if you have HIV. If you are a woman who has or will have a baby, talk with your doctor about the best way to feed your baby. You should be aware that if your baby does not already have HIV, there is a chance that HIV can be transmitted through breast-feeding.

- *If you have liver problems:* If you have liver problems or are infected with Hepatitis B or Hepatitis C, you should tell your doctor before taking KALETRA.

- *If you have diabetes:* Some people taking protease inhibitors develop new or more serious diabetes or high blood sugar. Tell your doctor if you have diabetes or an increase in thirst or frequent urination.

- *If you have hemophilia:* Patients taking KALETRA may have increased bleeding.

How do I store KALETRA?

- Keep KALETRA and all other medicines out of the reach of children.

- Refrigerated KALETRA capsules and oral solution remain stable until the expiration date printed on the label. If stored at room temperature up to 77°F (25°C), KALETRA capsules and oral solution should be used within 2 months.

Do not keep medicine that is out of date or that you no longer need. Be sure that if you throw any medicine away, it is out of the reach of children.

General advice about prescription medicines:

Talk to your doctor or other health care provider if you have any questions about this medicine or your condition. Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. If you have any concerns about this medicine, ask you doctor. Your doctor or pharmacist can give you information about this medicine that was written for health care professionals. Do not use this medicine for a condition for which it was not prescribed. Do not share this medicine with other people.

* The brands listed are trademarks of their respective owners and are not trademarks of Abbott Laboratories. The makers of these brands are not affiliated with and do not endorse Abbott Laboratories or its products.

Revised: New

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Division of Antiviral Drug Products (DAVDP)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration

TELEFACSIMILE TRANSMISSION RECORD

To: Becky Welch

Fax Number: (847) 937-8002

Date: September 15, 2000

Company: Abbott Labs

No. of pages (excluding cover): 6

Message: Approval letter for Kaletra

From: Sylvia D. Lynche, PharmD

Telephone: (301) 827- 2335

Fax Number: (301) 827-2471

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Rockville, Maryland 20850

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-226
NDA 21-251

SEP 15 2000

Abbott Laboratories
Attention: Rebecca A. Welch
Associate Director, PPD Regulatory Director
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 66064-6108

Dear Ms. Welch:

Please refer to your new drug applications (NDA) both dated May 31, 2000, received June 1, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for KALETRA (400 mg lopinavir/100 mg ritonavir) oral capsules and KALETRA (80mg lopinavir/20mg ritonavir) oral solution.

The User Fee goal date for these applications is December 1, 2000.

We acknowledge receipt of your submissions dated:

December 28, 1999	June 21, 2000	September 7, 2000
January 12, 2000	June 28, 2000	September 13, 2000
March 31, 2000	July 7, 2000	September 14, 2000
April 10, 2000	July 27, 2000 (2)	September 15, 2000 (3)
May 17, 2000	August 2, 2000	
May 31, 2000	August 7, 2000	
June 7, 2000	August 16, 2000	
June 9, 2000	August 30, 2000	

These new drug applications provide for the use of KALETRA in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients age six months and older.

We have completed the review of these applications, as amended, according to the regulations for accelerated approval, and have concluded that adequate information has been presented to approve KALETRA for use as recommended in the agreed upon draft label dated September 15, 2000. Accordingly, these applications are approved under 21 CFR 314 subpart H. Approval is effective on the date of this letter. Marketing of these drug products and related activities are to be in accordance with the substance and procedures of the referenced accelerated approval regulations.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted September 15, 2000, patient package insert submitted September 15, 2000, immediate container and carton labels submitted September 15, 2000). Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, these submission should be designated **"FINAL PRINTED LABELING"** for approved NDA 21-226 and 21-251. Approval of this submission by FDA is not required before the labeling is used.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your post marketing studies (Subpart H) as specified in your submission dated September 15, 2000, in which you agreed to submit the results from the final study analyses of the following two ongoing phase 3 studies of the safety and efficacy of KALETRA to support traditional approval: Study M98-863, "A Randomized, Double-Blind, Phase III Study of ABT-378/Ritonavir Plus Stavudine and Lamivudine vs. Nelfinavir Plus Stavudine and Lamivudine in Antiretroviral-Naïve HIV-Infected Subjects" and Study M98-888, "A Randomized, Open-Label, Phase III Study of ABT-378/ritonavir in Combination with Nevirapine and Two Nucleoside Reverse Transcriptase Inhibitors vs Investigator Selected Protease Inhibitor(s) in Combination with Nevirapine and Two NRTIs in Antiretroviral-Experienced HIV-Infected Subjects".

Final study reports should be submitted to these NDAs as a supplemental application. For administrative purposes, all submissions relating to this Phase 4 commitment must be clearly designated "Subpart H".

In addition, we note your following Phase 4 commitments, specified in your submission dated September 15, 2000. These commitments, along with any completion dates agreed upon, include:

Phase 4 Commitments:

Chemistry

1. A commitment to reassess the drug substance specification and the drug product specification when stability studies on the first three commercial scale lots of the capsules have been completed. During this reassessment, release and stability data from both commercial and representative NDA lots will be considered. The applicant will submit this data, with the proposed specifications, through a prior approval supplement to NDA 21-226.

Projected Submission date: First quarter 2003.

2. A commitment to reassess the drug product specification when stability studies on the first three commercial scale lots of the oral solution have been completed. During this reassessment, release and stability data from both commercial and representative NDA lots will be considered. The applicant will submit this data, with the proposed specifications, through a prior approval supplement to NDA 21-251.

   Projected Submission date: First quarter 2003.

Microbiology

3. Analyze isolates from patients with virologic failure on KALETRA to determine associations between protease mutations and *in vitro* shifts in susceptibility to define the resistance profile of lopinavir.

   Projected Submission Date: Based on the availability of isolates, by fourth quarter 2001; data would be provided by second quarter 2002.

4. Continue genotypic and phenotypic analysis of isolates from patients in ongoing Studies M97-765 and M98-957 who experience loss of virologic response.

   Projected Submission Date: Second quarter 2001.

5. Assess the genotypic basis of drug susceptibility attributable to extragenic sites, such as the protease cleavage sites.

   Projected Submission Date: Second quarter 2001.

6. Conduct *in vitro* combination activity studies.

   Projected Submission Date: Third quarter 2001.

7. Evaluate the cross-resistance potential between KALETRA and amprenavir.

   Projected Submission Date: Based on the availability of isolates, by fourth quarter 2001; data would be completed by second quarter 2002.

Pharmacology/toxicology

8. Continue carcinogenicity studies and submit final reports.

   Projected Submission Date: Fourth quarter 2001.

Clinical Pharmacology

9. Evaluate KALETRA pharmacokinetics in subjects with mild and moderate hepatic impairment, to allow the determination of dosing recommendations, through the conduct of a pharmacokinetic study.

   Projected Submission Date: Third quarter 2002.

10. Establish appropriate dosing recommendations for the coadministration of KALETRA with other approved protease inhibitors through the conduct of drug interaction studies.

    Projected Submission Date: Third quarter 2002.

11. Determine, *in vivo*, the extent to which KALETRA inhibits CYP2D6. Consideration will be given to conducting a drug interaction study with KALETRA and desipramine.

    Projected Submission Date: First quarter 2002.

12. Further evaluation of the pharmacokinetics of KALETRA and nevirapine in HIV-infected adults from Study M97-765

    Projected Submission Date: First quarter 2002.

13. Explore dosing recommendations for coadministration of KALETRA and rifampin, with additional ritonavir.

    Projected Submission Date: Third quarter 2002.

14. Explore dosing recommendations for the coadministration of KALETRA plus approved protease inhibitor(s) plus efavirenz/nevirapine through analysis of data from the Expanded Access Program.

    Projected Submission Date: Third quarter 2001.

15. Evaluate pharmacokinetic/pharmacodynamic relationships in Studies M98-957 and M99-049.

    Projected Submission Date: Data for M98-957 by second quarter 2001; based on enrollment projection, 48 week data from M99-049 should be available third quarter 2002.

Clinical

16. Continue to investigate the efficacy of once daily administration of KALETRA through the conduct of Study M99-056.

    Projected Submission Date: Fourth quarter 2001.

17. Continue to evaluate the activity of higher doses of KALETRA in patients exhibiting virologic failure or showing reduced susceptibility to multiple protease inhibitors through the conduct of Study M99-049.

    Projected Submission Date: Based on enrollment projection, the 48 week report should be available third quarter 2002.

18. Development of educational materials for patients and healthcare workers regarding avoidance of drug interactions.

    Projected Submission Date: Ongoing commitment to provide this information.

19. Continued evaluation of suspected protease inhibitor class adverse events including (a) establishment of an intercompany collaboration, or company based registry to collect data on patients who develop fractures or avascular hip necrosis while receiving antiretroviral therapy and (b) fat redistribution. This will include investigation of mechanisms for development of fat redistribution in patients receiving protease inhibitors, the incidence of this event, and the potential for long-term consequences. In addition, ongoing and future clinical trials should provide appropriate monitoring for these events and for any lipid-related disorders.

    Projected Submission Date: Ongoing commitment with update provided no later than third quarter 2002.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to these NDAs. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to these NDAs as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to these NDAs. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments".

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as

advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27) for pediatric patients under the age of 6 months. Accordingly, we are deferring submission of your studies in pediatric patients under the age of 6 months until June 1, 2003.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). Please refer to the Pediatric Written Request dated March 31, 1999. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Sylvia D. Lynche, PharmD, Regulatory Management Officer, at (301) 827-2335.

Sincerely,

Sandra L. Kweder M.D. 9-15-00

Sandra L. Kweder, M.D.
Acting Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

US005886036A

United States Patent [19]

Kempf et al.

[11] Patent Number: 5,886,036

[45] Date of Patent: Mar. 23, 1999

[54] RETROVIRAL PROTEASE INHIBITING COMPOUNDS

[75] Inventors: Dale J. Kempf, Libertyville; Daniel W. Norbeck, Crystal Lake; Hing Leung Sham; Chen Zhao, both of Gurnee, all of Ill.

[73] Assignee: Abbott Laboratories, Abbott Park, Ill.

[21] Appl. No.: 822,071

[22] Filed: Mar. 20, 1997

Related U.S. Application Data

[62] Division of Ser. No. 413,136, Mar. 29, 1995, Pat. No. 5,674,882, which is a division of Ser. No. 158,587, Dec. 2, 1993, abandoned, which is a continuation-in-part of Ser. No. 998,114, Dec. 29, 1992, abandoned.

[51] Int. Cl.[6] A61K 31/425; A61K 31/235

[52] U.S. Cl. 514/533; 514/365

[58] Field of Search 514/533

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9118866	12/1991	WIPO .
9206996	4/1992	WIPO .
9220665	11/1992	WIPO .
9301174	1/1993	WIPO .

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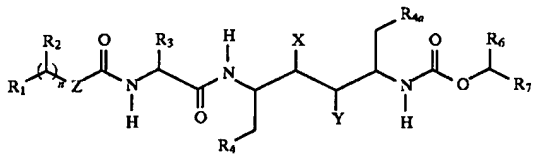
Attorney, Agent, or Firm—Steven R. Crowley

[57] ABSTRACT

A retroviral protease inhibiting compound of the formula:



is disclosed.

19 Claims, No Drawings

—NHR_{8a} wherein R_{8a} is hydrogen, loweralkyl or an N-protecting group; or a pharmaceutically acceptable salt, ester or prodrug thereof.

Preferred compounds of the formula A are those wherein R_1 is monosubstituted thiazolyl or monosubstituted oxazolyl; n is 1; R_2 is hydrogen; R_4 is phenyl or thiazolyl; R_{4a} is phenyl; R_6 is hydrogen and R_7 is thiazolyl, oxazolyl, isothiazolyl or isoxazolyl.

More preferred compounds of the formula A are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl; n is 1; R_2 is hydrogen; R_4 is phenyl; R_{4a} is phenyl; R_6 is hydrogen and R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl.

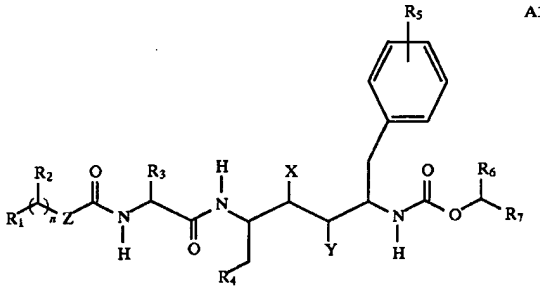
Even more preferred compounds of the formula A are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is loweralkyl; n is 1; R_2 is hydrogen; R_4 is phenyl; R_{4a} is phenyl; R_6 is hydrogen; R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; and Z is —O— or —$N(R_8)$— wherein R_8 is loweralkyl.

Most preferred compounds of the formula A are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is ethyl or isopropyl; n is 1; R_2 is hydrogen; R_3 is methyl or isopropyl; R_4 is phenyl; R_{4a} is phenyl; R_6 is hydrogen; R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; and Z is —O—.

Most preferred compounds of the formula A are also those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is ethyl or isopropyl; n is 1; R_2 is hydrogen; R_3 is isopropyl; R_4 is phenyl; R_{4a} is phenyl; R_6 is hydrogen; R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; and Z is —$N(R_8)$— wherein R_8 is methyl.

Most preferred compounds of the formula A are also those wherein the configuration of the carbon atom bearing —CH_2R_4 is "S" and the configuration of the carbon bearing X is "S" when X is —OH and the configuration of the carbon atom bearing Y is "S" when Y is —OH and the configuration of the carbon atom bearing —CH_2(R_5-substituted phenyl) is "S".

Preferred compounds of the invention are compounds of the formula



A1

wherein R_1 is monosubstituted thiazolyl, monosubstituted oxazolyl, monosubstituted isoxazolyl or monosubstituted isothiazolyl wherein the substituent is selected from (i) loweralkyl, (ii) loweralkenyl, (iii) cycloalkyl, (iv) cycloalkylalkyl, (v) cycloalkenyl, (vi) cycloalkenylalkyl, (vii) heterocyclic wherein the heterocyclic is selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyridazinyl and pyrazinyl and wherein the heterocyclic is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (viii) (heterocyclic)alkyl wherein heterocyclic is defined as above, (ix) alkoxyalkyl, (x) thioalkoxyalkyl, (xi) alkylamino, (xii) dialkylamino, (xiii) phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (xiv) phenylalkyl wherein the phenyl ring is unsubstituted or substituted as defined above, (xv) dialkylaminoalkyl, (xvi) alkoxy and (xvii) thioalkoxy;

n is 1, 2 or 3;

R_2 is hydrogen or loweralkyl;

R_3 is loweralkyl;

R_4 is phenyl, thiazolyl or oxazolyl wherein the phenyl, thiazolyl or oxazolyl ring is unsubstituted or substituted with a substituent selected from (i) halo, (ii) loweralkyl, (iii) hydroxy, (iv) alkoxy and (v) thioalkoxy;

R_5 is hydrogen, halo, loweralkyl, hydroxy, alkoxy or thioalkoxy;

R_6 is hydrogen or loweralkyl;

R_7 is thiazolyl, oxazolyl, isoxazolyl or isothiazolyl wherein the thiazolyl, oxazolyl, isoxazolyl or isothiazolyl ring is unsubstituted or substituted with loweralkyl;

X is hydrogen and Y is —OH or X is —OH and Y is hydrogen, with the proviso that X is hydrogen and Y is —OH when Z is —$N(R_8)$— and R_7 is unsubstituted and with the proviso that X is hydrogen and Y is —OH when R_3 is methyl and R_7 is unsubstituted;

Z is absent, —O—, —S—, —CH_2— or —$N(R_8)$— wherein R_8 is loweralkyl, cycloalkyl, —OH or —NHR_{8a} wherein R_{8a} is hydrogen, loweralkyl or an N-protecting group; or a pharmaceutically acceptable salt, ester or prodrug thereof.

Preferred compounds of the formula A1 are those wherein R_1 is monosubstituted thiazolyl or monosubstituted oxazolyl; n is 1; R_2 is hydrogen; R_4 is phenyl or thiazolyl; R_5 is hydrogen; R_6 is hydrogen and R_7 is thiazolyl, oxazolyl, isothiazolyl or isoxazolyl.

More preferred compounds of the formula A1 are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl; n is 1; R_2 is hydrogen; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen and R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl.

Even more preferred compounds of the formula A1 are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is loweralkyl; n is 1; R_2 is hydrogen; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen; R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; and Z is —O— or —$N(R_8)$— wherein R_8 is loweralkyl.

Most preferred compounds of the formula A1 are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is ethyl or isopropyl; n is 1; R_2 is hydrogen; R_3 is methyl or isopropyl; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen; R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; and Z is —O—.

Most preferred compounds of the formula A1 are also those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is ethyl or isopropyl; n is 1; R_2 is hydrogen; R_3 is isopropyl; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen; R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; and Z is —$N(R_8)$— wherein R_8 is methyl.

The term "O-protecting group" as used herein refers to a substituent which protects hydroxyl groups against undesirable reactions during synthetic procedures such as those O-protecting groups disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)). O-protecting groups comprise substituted methyl ethers, for example, methoxymethyl, benzyloxymethyl, 2-methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, t-butyl, benzyl and triphenylmethyl; tetrahydropyranyl ethers; substituted ethyl ethers, for example, 2,2,2-trichloroethyl; silyl ethers, for example, trimethylsilyl, t-butyidimethylsilyl and t-butyldiphenylsilyl; and esters prepared by reacting the hydroxyl group with a carboxylic acid, for example, acetate, propionate, benzoate and the like.

The term "loweralkyl" as used herein refers to straight or branched chain alkyl radicals containing from 1 to 6 carbon atoms including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl and the like.

The term "loweralkenyl" as used herein refers to a straight or branched chain alkyl radical containing from 2 to 6 carbon atoms and also having one carbon-carbon double bond including, but not limited to, vinyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl and the like.

The term "phenyl" as used herein refers to a phenyl group which is unsubstituted or substituted with a substituent selected from loweralkyl, alkoxy, thioalkoxy, hydroxy and halo.

The term "phenylalkyl" as used herein refers to an phenyl group appended to a loweralkyl radical including, but not limited to, benzyl, 4-hydroxybenzyl, 4-chlorobenzyl, 1-naphthylmethyl and the like.

The term "alkylamino" as used herein refers to a loweralkyl radical appended to an —NH radical.

The term "cycloalkyl" as used herein refers to an aliphatic ring having 3 to 7 carbon atoms including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl and the like. A preferred cycloalkyl group is cyclopropyl

The term "cycloalkylalkyl" as used herein refers to a cycloalkyl group appended to a loweralkyl radical, including but not limited to cyclohexylmethyl.

The term "cycloalkenyl" as used herein refers to to an aliphatic ring having 5 to 7 carbon atoms and also having one carbon-carbon double bond including, but not limited to, cyclopentenyl, cyclohexenyl and the like.

The term "cycloalkenyalkyl" as used herein refers to a cycloalkenyl group appended to a loweralkyl radical including, but not limited to, cyclopentenylmethyl, cyclohexenylmethyl and the like.

The terms "alkoxy" and "thioalkoxy" as used herein refer to $R_{15}O$— and $R_{15}S$—, respectively, wherein R_{15} is a loweralkyl group or benzyl.

The term "alkoxyalkyl" as used herein refers to an alkoxy group appended to a loweralkyl radical.

The term "thioalkoxyalkyl" as used herein refers to a thioalkoxy group appended to a loweralkyl radical.

The term "dialkylamino" as used herein refers to —$NR_{16}R_{17}$ wherein R_{16} and R_{17} are independently selected from loweralkyl groups.

The term "dialkylaminoalkyl" as used herein refers to —$NR_{18}R_{19}$ which is appended to a loweralkyl radical wherein R_{18} and R_{19} are independently selected from loweralkyl.

The term "halo" or "halogen" as used herein refers to —Cl, —Br, —I or —F.

The term "heterocyclic" as used herein refers to a heterocyclic group selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyridazinyl and pyrazinyl and wherein the heterocyclic is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy.

The term "(heterocyclic)alkyl" as used herein refers to a heterocyclic group appended to a loweralkyl radical including, but not limited to, pyrrolidinylmethyl and morpholinylmethyl.

The term "activated ester derivative" as used herein refer to acid halides such as acid chlorides, and activated esters including, but not limited to, formic and acetic acid derived anhydrides, anhydrides derived from alkoxycarbonyl halides such as isobutyloxycarbonylchloride and the like, N-hydroxysuccinimide derived esters, N-hydroxyphthalimide derived esters, N-hydroxybenzotriazole derived esters, N-hydroxy-5-norbornene-2,3-dicarboxamide derived esters, 2,4,5-trichlorophenol derived esters and the like.

In the compounds of the invention, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. As used herein, the term "stable compound" refers to a compound that is sufficiently stable to survive isolation to a useful degree of purity from a reaction mixture and formulation into a therapeutic dosage form suitable for administration.

Preferred compounds of the invention are selected from the group consisting of:

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)methoxycarbonyl)valinyl)-amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

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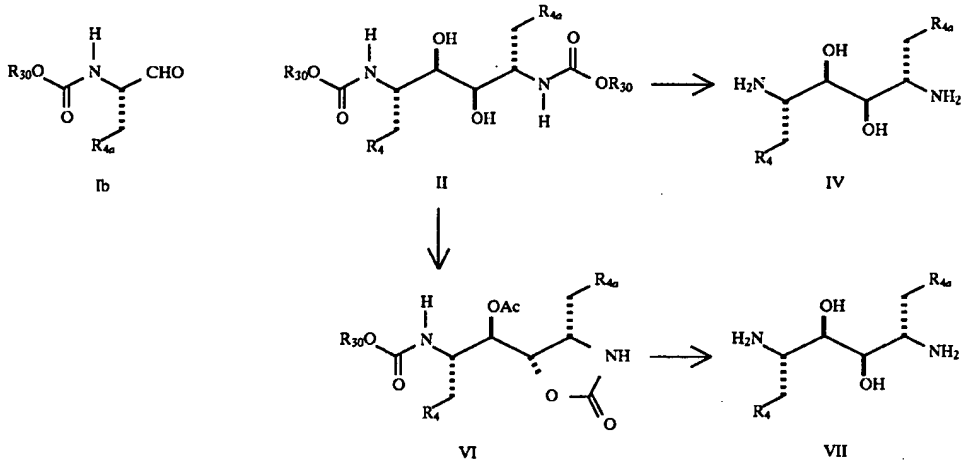
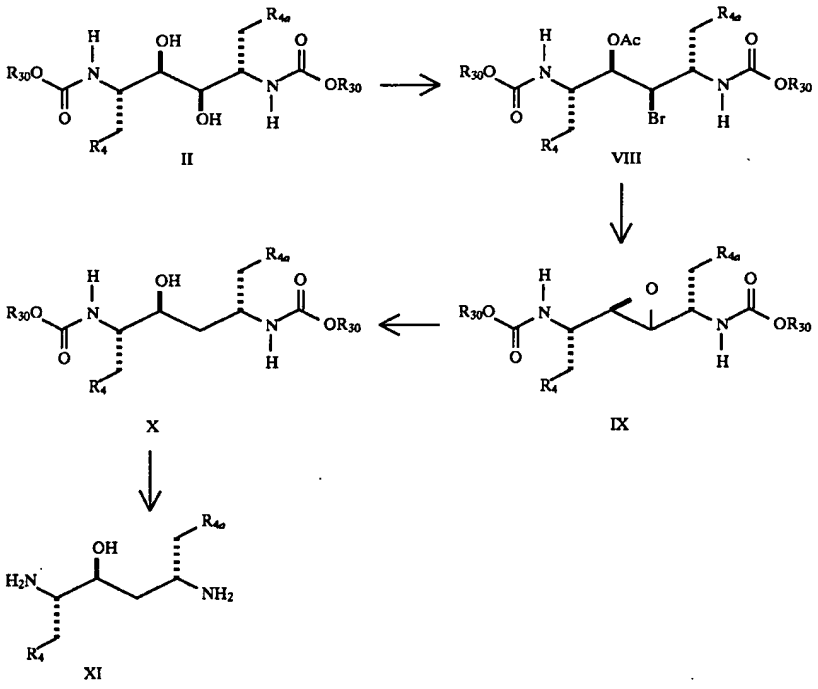
Scheme 1



As outlined in Scheme 2, treatment of compound II with α-acetoxy-isobutyryl bromide in hexane/dichloromethane produces bromoacetate VIII. Hydrolysis of VIII with concommitant cyclization produces epoxide IX, which is reduced with sodium borohydride and trifluoroacetic acid to produce compound X. Barium hydroxide hydrolysis of X leads to diamine XI.

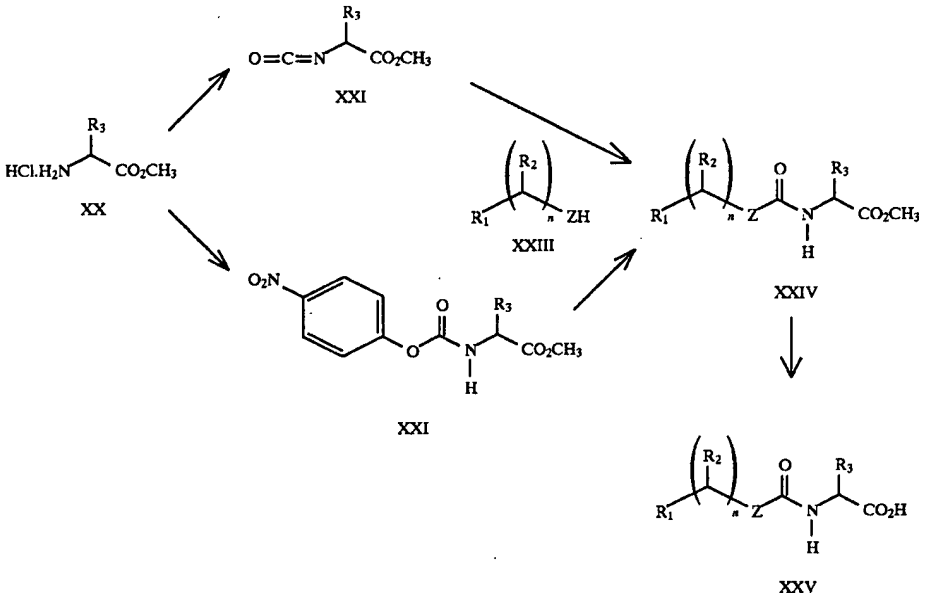
Scheme 2



As outlined in Scheme 3, acylation of the enolate derived from compound XII with ethyl chloroformate gives compound XIII. Subsequent alkylation of the enolate prepared from XIII provides compound XIV (R_{4a} is thiazolyl), which is hydrolyzed and decarboxylated to lactone XV. Hydrolysis of XV and protection of the hydroxyl group leads to compound XVI, which, upon treatment with diphenylphosphoryl azide undergoes a Curtius rearrangement. The intermediate isocyanate is trapped with benzyl alcohol to produce compound XVII. Desilylation of XVII with tetrabutylammonium fluoride provides compound XVIII, which is deprotected with HBr to give diamine XIX.

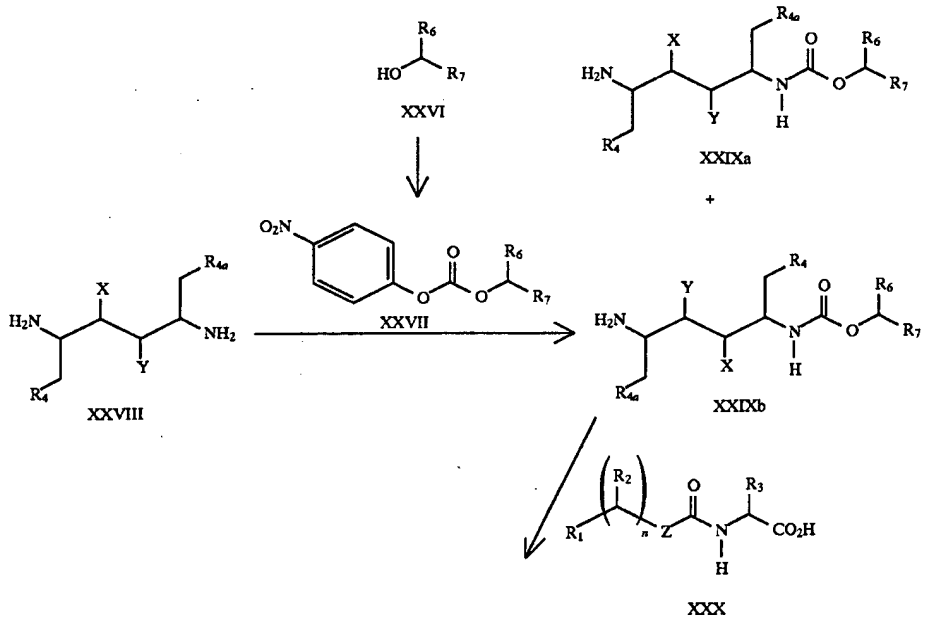
In a preferred embodiment of the process shown in Scheme 3, R_4 is phenyl.

Scheme 4



As outlined in Scheme 5, compound XXVIII, which represents diamines IV, V, VII, XI and XIX, is acylated with an activated derivative of XXVI having the formula $(R_6)(R_7)CHOC(O)OL$ wherein L is an activating group for the acylation reaction such as p-nitrophenyl, phenyl, N-succinimidyl, N-phthalimidyl, N-benzotriazolyl, N-5-norbornene-2,3-carboxamidyl or 2,4,5-trichlorophenyl and the like (for example, XXVII, which is prepared by reacting XXVI with 4-nitrophenyl chloroformate) to provide a mixture of compounds XXIX*a* and XXIX*b* or an acid addition salt thereof. Coupling of XXIX*a* or XXIX*b* to compound XXX by treatment with a carbodiimide (or by reaction with an activated ester of XXX) produces compound XXXI*a* or XXXI*b*, respectively. In a preferred embodiment of the process shown in Scheme 5, n is 1, R_4 and R_{4a} are each phenyl, X is H and Y is OH.

Scheme 5



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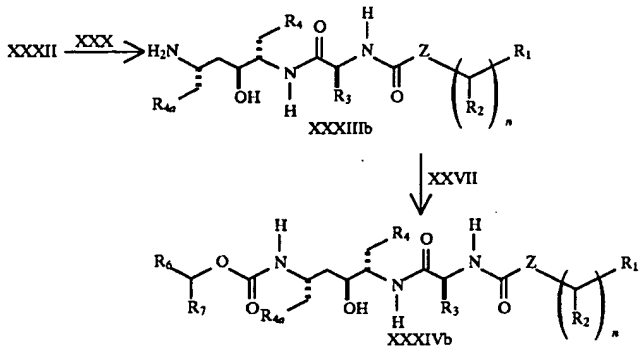
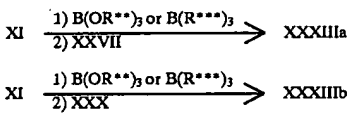
Scheme 6A



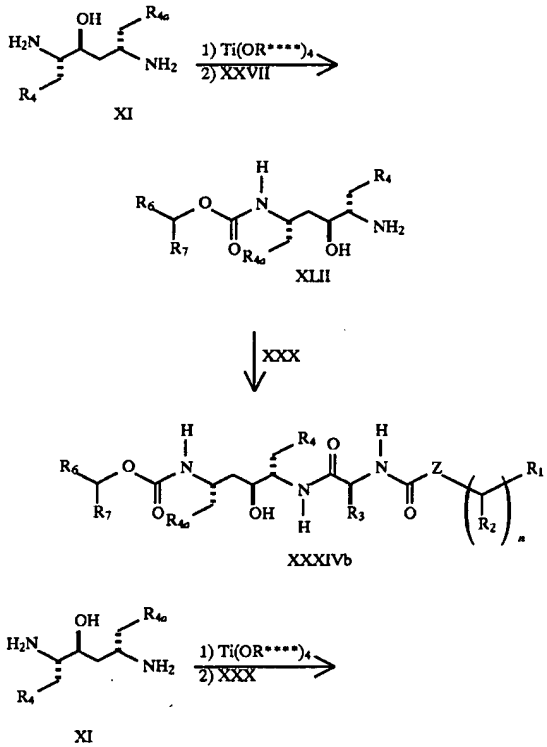
Scheme 6B outlines an alternative preparation of XXXIII*a* or XXXIII*b*. Reaction of compound Xi with (i) two equivalents of $B(OR^{**})_3$ wherein R^{**} is loweralkyl (preferably, isopropyl) or (ii) two equivalents of $B(R^{***})_3$ wherein R^{***} is halo (preferably, fluoro) and four equivalents of an amine such as triethylamine in an inert solvent such as tetrahydrofuran, followed by reaction with an activated derivative of XXVI having the formula $(R_6)(R_7)$ CHOC(O)OL wherein L is an activating group for the acylation reaction such as p-nitrophenyl, phenyl, N-succinimidyl, N-phthalimidyl, N-benzotriazolyl, N-5-norbornene-2,3-carboxamidyl or 2,4,5-trichlorophenyl and the like (for example, XXVII), gives compound XXXIII*a* or an acid addition salt thereof. Similarly, reaction of compound XI with two equivalents of $B(OR^{**})_3$ wherein R^{**} is loweralkyl (preferably, isopropyl) or two equivalents of $B(R^{***})_3$ wherein R^{***} is halo (preferably, fluoro), followed by reaction with compound XXX (or an activated ester derivative thereof), gives compound XXXIII*b* or an acid addition salt thereof. In the preferred embodiment of the process shown in Scheme 6B, n is 1, R_4 and R_{4a} are each phenyl and R^{**} is isopropyl or R^{***} is fluoro.

Scheme 6B

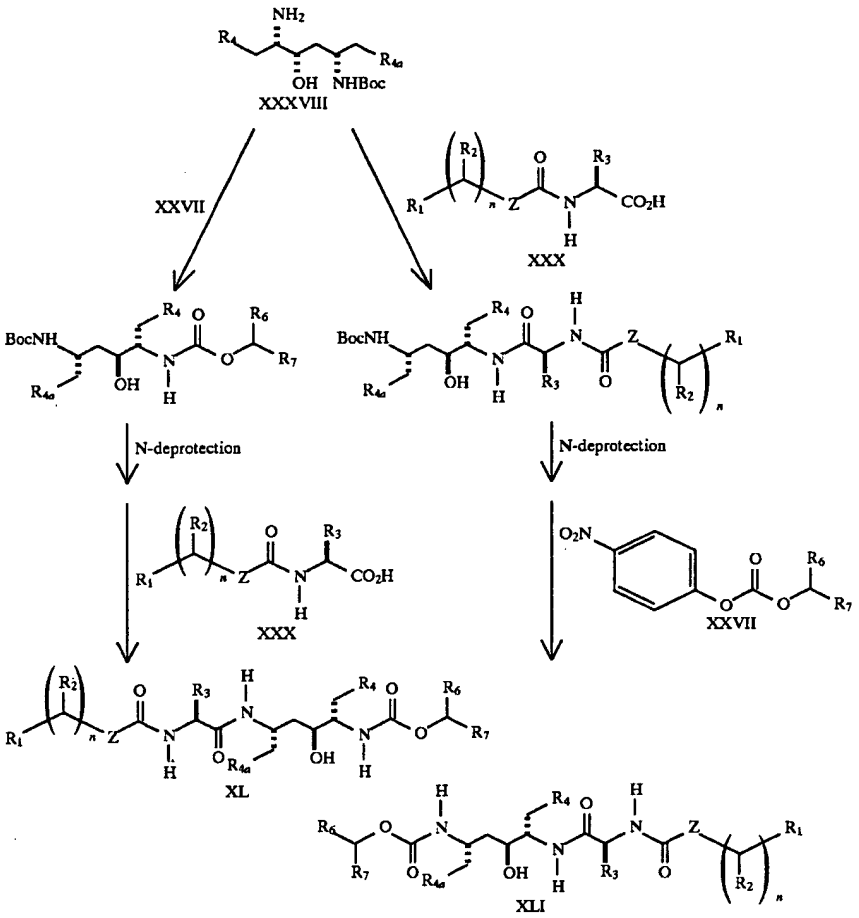


Scheme 6C outlines an alternative preparation of XXXIV*a* and XXXIV*b*. Reaction of compound XI with two molar equivalents of $Ti(OR^{****})_4$ wherein R_4 is loweralkyl (preferably, isopropyl), followed by reaction with an activated derivative of XXVI having the formula $(R_6)(R_7)$ CHOC(O)OL wherein L is an activating group for the acylation reaction such as p-nitrophenyl, phenyl, N-succinimidyl, N-phthalimidyl, N-benzotriazolyl, N-5-norbornene-2,3-carboxamidyl or 2,4,5-trichlorophenyl and the like (for example, XXVII), provides compound XLII or an acid addition salt thereof. Reaction of compound XLII with compound XXX (or an activated ester derivative thereof) gives compound XXXIV*b*. Similarly, reaction of compound Xi with two molar equivalents of $Ti(OR^{****})_4$ wherein R_4 is loweralkyl (preferably, isopropyl), followed by reaction with compound XXX (or an activated ester derivative thereof), provides compound XLIII or an acid addition salt thereof. Reaction of compound XLIII with an activated derivative of XXVI having the formula $(R_6)(R_7)$ CHOC(O)OL wherein L is an activating group for the acylation reaction such as p-nitrophenyl, phenyl, N-succinimidyl, N-phthalimidyl, N-benzotriazolyl, N-5-norbornene-2,3-carboxamidyl or 2,4,5-trichlorophenyl and the like (for example, XXVII) gives compound XXXIV*a*. In the preferred embodiment of the process shown in Scheme 6C, n is 1, R_4 and R_{4a} are each phenyl and R^{****} is isopropyl.

Scheme 6C



Scheme 9



The following examples will serve to further illustrate the preparation of the novel compounds of the invention.

EXAMPLE 1

A. N-(((Benzyl)oxy)carbonyl)-L-phenylalaninal

A solution of 24.5 ml of anhydrous dimethyl sulfoxide in 870 ml of anhydrous dichloromethane was cooled under N_2 atmosphere to −60° C. and treated over a period of 15 min with 131 ml of a 2M solution of oxalyl chloride in dichloromethane in order that the internal temperature remained below −50° C. After addition, the solution was stirred at −60° C. for 15 min and treated over a period of 20 min with a solution of 50 g (0.175 mol) of N-(((benzyl)oxy)-carbonyl)-L-phenylalaninol in 200 ml of dichloromethane. The resulting solution was stirred at −60° C. for 1 h, then treated over a period of 15 min with 97 ml of triethylamine in order that the internal temperature remained below −50° C. After addition the solution was stirred at −60° C. for 15 min, then, with the cooling bath in place, was treated rapidly (over a period of 1 min) with a solution of 163 g of citric acid in 550 ml of water. The resulting slurry was stirred vigorously for 10 min, allowed to warm, diluted to 1 liter with water, and separated. The organic layer was washed with 700 ml of water followed by a mixture of 550 ml of water and 150 ml of saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo at 20° C. to give the crude desired compound as a light yellow solid.

B. (2S,3R,4R,5S)-2,5-Bis-(N-(((benzyl)oxy) carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane and (2S,3S,4S,5S)-2,5-Bis-(N-(((benzyl)oxy) carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane

A suspension of 78.5 g of VCl3. (tetrahydrofuran)$_3$ and 16 g of zinc dust in 400 ml of dry dichloromethane was stirred under N_2 atmosphere for 1 h at 25° C. A solution of 0.175 mol of N-(((benzyl)oxy)carbonyl)-L-phenylalaninal in 200 ml of dichloromethane was then added in one portion, and the resulting mixture was stirred at ambient temperature under N_2 atmosphere for 16 h. The resulting mixture was added to 500 ml of 1M aqueous HCl, diluted with 500 ml of hot chloroform, and shaked vigorously for 2 min. The layers were separated, and the organic layer was washed with 1M aqueous HCl and separated. Filtration of the organic phase provided the crude desired product as a solid residue. The residue was slurried in 1.25 liters of acetone, treated with 5 ml of concentrated H_2SO_4, and stirred for 16 h at ambient temperature. The resulting mixture was filtered, and the residue (residue A) was washed with 50 ml of acetone. The combined filtrate was concentrated to a volume of 250 ml,

with diethyl ether and cooled in an ice bath. Then, the pH was lowered to approximately 3 using 6N HCl. The organic phase was separated, and the aqueous layer was washed 3 times with diethyl ether. The combined ethereal portions were dried over $NaSO_4$, and concentrated in vacuo. The crude desired compound was stored at −30° C. and used without further purification.

J. Ethyl Thiazole-5-carboxylate

To a round bottom flask was added 250 mL of dry acetone, 7.5 g (0.123 mol) of thioformamide, and 18.54 g (0.123 mol) of ethyl 2-chloro-2-formylacetate. The reaction was heated at reflux for 2 hours. The solvent was removed in vacuo, and the residue was purified by chromatography (SiO_2, 6 cm o.d. column, 100% $CHCl_3$, R_f=0.25) to provide 11.6 g (60%) of the desired compound as a light yellow oil. NMR ($CDCl_3$) δ 1.39 (t, J=7 Hz, 3H), 4.38 (q, J=7 Hz, 2H), 8.50 (s, 1H), 8.95 (s, 1H).

K. 5-(Hydroxymethyl)thiazole

To a precooled (ice bath) three neck 500 mL flask containing lithium aluminum hydride (76 mmol) in 250 mL of THF was added ethyl thiazole-5-carboxylate (11.82 g, 75.68 mmol) in 100 mL of THF dropwise over 1.5 hours to avoid excess foaming. The reaction was stirred for an additional hour, and treated cautiously with 2.9 mL of water, 2.9 mL of 15% NaOH, and 8.7 mL of water. The solid salts were filtered, and the filtrate set aside. The crude salts were heated at reflux in 100 mL of ethyl acetate for 30 min. The resulting mixture was filtered, and the two filtrates were combined, dried over Na_2SO_4, and concentrated in vacuo. The product was purified by silica gel chromatography eluting sequentially with 0%–2%–4% methanol in chloroform, to provide the desired compound, Rf=0.3 (4% methanol in chloroform), which solidified upon standing in 75% yield. NMR ($CDCl_3$) δ 4.92 (s, 2H), 7.78 (s, 1H), 8.77 (s, 1H). Mass spectrum: $(M+H)^+$=116.

L. ((5-Thiazolyl)methyl)-(4-nitrophenyl)carbonate

A solution of 3.11 g (27 mmol) of 5-(hydroxymethyl) thiazole and excess N-methyl morpholine in 100 ml of methylene chloride was cooled to 0° C. and treated with 8.2 g (41 mmol) of 4-nitrophenyl chloroformate. After being stirred for 1 h, the reaction mixture was diluted with $CHCl_3$, washed successively with 1N HCl, saturated aqueous $NaHCO_3$, and saturated brine, dried over $NaSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (SiO_2, 1–2% MeOH/$CHCl_3$, Rf=0.5 in 4% MeOH/$CHCl_3$) to yield 5.9 g (78%) of the desired compound as a yellow solid. NMR ($CDCl_3$) δ 5.53 (s, 2H), 7.39 (dt, J=9, 3 Hz, 2H), 8.01 (s, 1H), 8.29 (dt, J=9, 3 Hz, 2H), 8.90 (s, 1H). Mass spectrum: $(M+H)^+$=281.

M. (2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane and (2S,3S,5S)-2-Amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

A solution of 500 mg (1.76 mmol) of (2S,3S,5S)-2,5-diamino-1,6-diphenyl-3-hydroxyhexane and 480 mg (1.71 mmol) of ((5-thiazolyl)methyl)-(4-nitrophenyl)carbonate in 20 ml of THF was stirred at ambient temperature for 4 h. After removal of the solvent in vacuo, the residue was purified by silica gel chromatography using first 2% then 5% methanol in chloroform to provide a mixture of the two desired compounds. Silica gel chromatography of the mixture using a gradient of 0–1–2% methanol in 93:2 isopropylamine:chloroform provided 110 mg (16%) of (2S,3S,5S) -5-amino-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (R_f 0.48, 96:2:2 chloroform:methanol:isopropylamine) and 185 mg (28%) of (2S,3S,5S)-2-amino-5-(N-((5-thiazolyl)methoxycarbonyl) amino)-1,6-diphenyl-3-hydroxyhexane (R_f 0.44, 96:2:2 chloroform:methanol:isopropylamine).

(2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl)methoxycarbonyl) amino)-1,6-diphenyl-3-hydroxyhexane: NMR ($CDCl_3$) δ 1.3–1.6 (m, 2H), 2.40 (dd, J=14, 8 Hz, 1H), 2.78 (dd, J=5 Hz, 1H), 2.88 (d, J=7 Hz, 2H), 3.01 (m, 1H), 3.72 (br q, 1H), 3.81 (br d, J=10 Hz, 1H), 5.28 (s, 2H), 5.34 (br d, J=9 Hz, 1H), 7.07 (br d, J=7 Hz, 2H), 7.15–7.35 (m, 8H), 7.87 (s, 1H), 8.80 (s, 1 H). Mass spectrum: $(M+H)^+$=426.

(2S,3S,5S)-2-Amino-5-(N-((5-thiazolyl)methoxycarbonyl) amino)-1,6-diphenyl-3-hydroxyhexane: NMR ($CDCl_3$) δ 1.55 (dt, J=14, 8 Hz, 1H), 1.74 (m, 1H), 2.44 (dd, J=15, 1 Hz, 1H), 2.75–3.0 (m, 4H), 3.44 (m, 1H), 4.00 (br t, 1H), 5.28 (m, 3H), 7.1–7.4 (m, 10H), 7.86 (s, 1H), 8.80 (s, 1H). Mass spectrum: $(M+H)^+$=426.

N. (2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

A solution of 40 mmol of crude (4S,6S,1'S)-6-(1-amino-2-phenylethyl)-4-benzyl-2-phenyl-3-aza-2-bora-1-oxacyclohexane in 700 ml of anhydrous THF was cooled to −40° C. and treated dropwise over a period of 1 h with a solution of 7.83 g (27.9 mmol) of ((5-thiazolyl)methyl)-(4-nitrophenyl)carbonate in 300 ml of dry THF. The resulting solution was allowed to warm to 0° C. for 3 h, then to ambient temperature for 16 h. The solvent was removed in vacuo, and the residue was taken up in 700 ml of ethyl acetate, washed with three 150 ml portions of 1N aqueous NaOH and one 150 ml portion of brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by silica gel chromatography using methanol/chloroform mixtures provided the desired compound mixed with its regioisomer. A second chromatography using 1–3% isopropylamine in chloroform provided 5.21 g of the desired compound which solidified upon standing.

O. 2-Methylpropane-thioamide

A suspension of 100 g (1.15 mol) of isobutyramide in 4 L of diethyl ether was stirred vigorously and treated in portions with 51 g (0.115 mol) of P_4S_{10}. The resulting mixture was stirred at ambient temperature for 2 h, filtered, and concentrated in vacuo to provide 94.2 g (80%) of the crude desired compound. ^1H NMR (DMSO-d_6) δ 1.08 (d, J=7 Hz, 6H), 2.78 (heptet, J=7 Hz, 1H), 9.06 (br, 1H), 9.30 (br, 1H). Mass spectrum: $(M+H)^+$=104.

P. 4-(Chloromethyl)-2-isopropylthiazole hydrochloride

A mixture of 94.0 g (0.91 mol) of 2-methylpropane-thioamide, 115.7 g (0.91 mol) of 1,3-dichloroacetone, and 109.7 g (0.91 mol) of $MgSO_4$ in 1.6 liters of acetone was heated at reflux for 3.5 h. The resulting mixture was allowed to cool, filtered, and the solvent was removed in vacuo to provide the crude desired compound as a yellow oil. ^1H NMR (DMSO-d_6) δ 1.32 (d, J=7 Hz, 6H), 3.27 (heptet, J=7 Hz, 1H), 4.78 (s, 2H), 7.61 (s, 1H). Mass spectrum: $(M+H)^+$=176.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl) amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,2-dimethyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl) amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclopentyl) methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl) amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclohexyl)methyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-phenyl-4-thiazolyl) methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-benzyl-4-thiazolyl) methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl)ethyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl-1-ethenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl) amino)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(4-fluoro)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-chloro)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-methoxy)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N- Methyl-N-((2-(2-thiazolyl) methyl-4-thiazolyl)methyl)amino)carbonyl)valinyl) amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-methoxy-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethoxy-4-thiazolyl) methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyloxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(N,N-dimethylamino)methyl-4-thiazolyl)-methyl)amino) carbonyl)valinyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-pyrrolidinyl) methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl) amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-propyl-4-thiazolyl) methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl)propyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl)propyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-ethyl)propyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

EXAMPLE 3

A. N-(((4-nitrophenyl)oxy)carbonyl)-L-alanine Methyl Ester

Using the procedure of Example 1R, but replacing L-valine methyl ester hydrochloride with L-alanine methyl ester hydrochloride provided the desired compound (R_f 0.25, dichloromethane) in 95% yield.

B. N-((N-Methyl-N-((2-isopropyl-4-thiazolyl) methyl)amino)carbonyl)-L-alanine Methyl Ester

Using the procedure of Example 1S, but replacing N-((4-nitrophenyl)oxy)carbonyl)-L-valine methyl ester with the resultant compound of Example 3A provided, after silica gel chromatography using 97:3 CH_2Cl_2:CH_3OH, the desired compound (R_f 0.55, 95:5 CH_2Cl_2: CH_3OH) in 24% yield. ^1H NMR ($CDCl_3$) δ 1.39 (d, J=7 Hz, 6H), 1.43 (d, J=7 Hz, 3H), 2.98 (s, 3H), 3.28 (heptet, J=7 Hz, 1H), 3.74 (s, 3H), 4.46 (s, 2H), 4.49 (q, J=7 Hz, 1H), 6.12 (br, 1H), 6.98 (s, 1H). Mass spectrum: $(M+H)^+$=300.

C. N-((N-Methyl-N-((2-isopropyl-4-thiazolyl) methyl)amino)carbonyl)-L-alanine

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 3B provided the desired compound.

D. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino) carbonyl)-L-valine with the resultant compound of Example 3C provided, after silica gel chromatography using 97:3 CH_2Cl_2:CH_3OH, 70 mg (35%) of the desired compound (R_f 0.36, 95:5 CH_2Cl_2:CH_3OH), mp. 56°–58° C. Mass spectrum: $(M+H)^+$=693. Anal. Calcd for $C_{35}H_{44}N_6O_5S_2.0.5H_2O$: C, 59.89; H, 6.46; N, 11.97. Found: C, 60.07; H, 6.39; N, 12.00.

EXAMPLE 4

A. 2-Isopropyl-4-(((N-ethyl)amino)methyl)thiazole

Using the procedure of Example 1Q, but replacing 40% aqueous methylamine with 70% aqueous ethylamine pro-

(R_f 0.33, 10% methanol in chloroform), mp. 172°–174° C. Mass spectrum: $(M+H)^+$=708.

EXAMPLE 7

A. N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl) alanine Methyl Ester

A solution of 1.12 g (5.56 mmol) of 4-nitrophenyl chloroformate in 20 ml of CH_2Cl_2 was cooled to 0° C.and treated sequentially with 0.8 g (5.1 mmol) of 4-(hydroxymethyl)-2-isopropylthiazole and 0.6 ml (5.6 mmol) of 4-methylmorpholine. The resulting solution was stirred at 0° C. for 1 h, diluted with CH_2Cl_2, washed with three portions of aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo to give crude 2-isopropyl-4-(p-nitrophenyloxycarbonyloxymethyl)thiazole. A portion (0.53 g, 1.65 mmol) of the residue was taken up in 20 ml of chloroform, treated with 0.23 g (1.67 mmol) of L-alanine methyl ester hydrochloride and 0.36 ml (3.3 mmol) of 4-methylmorpholine, and heated at reflux for 16 h. After being allowed to cool, the solven was removed in vacuo, and the residue was purified by silica gel chromatography using 2% methanol in chloroform to provide 0.45 g (94%) of the desired compound, R_f 0.43 (5% methanol in CH_2Cl_2). ^1H NMR (DMSO-d_6) δ 1.26 (d, J=8 Hz, 3H), 1.32 (d, J=7 Hz, 6H), 3.27 (heptet, J=7 Hz, 1H), 3.63 (s, 3H), 4.10 (p, J=8 Hz, 1H), 5.02 (s, 2H), 7.47 (s, 1H), 7.81 (d, J=8 Hz, 1H). Mass spectrum: $(M+H)^+$=287.

B. N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl) alanine

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 7A provided the desired compound.

C. (2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl) methoxycarbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino) carbonyl)-L-valine with the resultant compound of Example 7B provided, after silica gel chromatography using 1% methanol in chloroform, 110 mg (69%) of the desired compound (R_f 0.4, 5% methanol in CH_2Cl_2), mp. 59°–61° C. Mass spectrum: $(M+H)^+$=680. Anal. Calcd for $C_{34}H_{41}N_5O_6S_2.0.5H_2O$: C, 59.28; H, 6.15; N, 10.17. Found: C, 59.37; H, 5.96; N, 10.18.

EXAMPLE 8

A. (5S,1'S)-5-(1-(tert-Butyloxycarbonylamino)-2-phenylethyl)-dihydrofuran-2(3H)-one

Prepared from commercially available ethyl-3-bromopropionate by using the procedure of A. E. DeCamp, et al., (*Tetrahedron Lett.* 1991, 32, 1867).

B. (5S,1'S)-5-(1-(tert-Butyloxycarbonylamino)-2-phenylethyl)-3-carboethoxy-dihydrofuran-2(3H)-one

Lithium diisopropylamide (LDA) was prepared by dropwise addition of 16.5 ml (41.2 mmol) of 2.5M n-BuLi to a solution of 5.8 ml (41.2 mmol) of diisopropyl amine in 30 ml of dry tetrahydrofuran at –78° C. The LDA solution was stirred for 30 min at –78° C. and 6.0 g (19.6 mmol) of the resultant compound of Example 8A in 30 ml of dry tetrahydrofuran was added dropwise. The reaction mixture was stirred for 30 min at –78° C. and 4.7 ml (49.1 mmol) of ethyl chloroformate was then added. After being stirred at –78° C. for 5 h, the reaction was quenched with saturated aqueous NH_4Cl, extracted with three 60 ml portions of dichloromethane. The combined organic layers were dried over Na_2SO_4, concentrated in vacuo and the residue was purified by silica gel chromatography using 25% ethyl acetate in hexane to provide 4.73 g (64%) of the desired compound as a white solid. Mass spectrum: $(M+H)^+$=378.

C. (5S,1'S)-5-(1-(tert-Butyloxycarbonylamino)-2-phenylethyl)-3-carboethoxy-3-((5-thiazolyl)methyl) dihydrofuran-2(3H)-one

Sodium metal (536 mg, 23.3 mmol) was dissolved in 10 ml of absolute ethanol. A solution of 4.0 g (10.6 mmol) of the resultant compound of Example 8B in 50 ml of absolute ethanol was added dropwise. The mixture was stirred at ambient temperature for 20 min and 5-chloromethylthiazole hydrochloride was then added. After being stirred at ambient temperature for 60 h, the reaction was cooled in an ice bath, neutralized with 10% citric acid to pH ~6 and extracted with four 50 ml portions of dichloromethane. The combined organic layers were dried over Na_2SO_4, concentrated in vacuo and the residue was purified by silica gel chromatography using 10% methanol in dichloromethane to provide 3.88 g (78%) of the desired compound as a white foamy solid. Mass spectrum: $(M+H)^+$=475.

D. (3S,5S,1'S)-5-(1-(tert-Butyloxycarbonylamino)-2-phenylethyl)-3-((5-thiazolyl)methyl)dihydrofuran-2(3H)-one

A solution of 3.88 g (8.18 mmol) of the resultant compound of Example 8C in 65 ml of dimethoxyethane was treated with 32.7 ml (32.7 mmol) of 1M aqueous lithium hydroxide. After being stirred at ambient temperature for 4 h, the bulk of the 1,2-dimethoxyethane was removed in vacuo. The remaining mixture was treated with 10% citric acid to pH 4–5 and extracted with four 50 ml portions of dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give the crude acid. The acid was dissolved in 50 ml of toluene, heated at reflux for 15 h. The solvent was removed in vacuo, and the residue was separated by silica gel chromatography using 50% ethyl acetate in hexane to provide 0.86 g (26%) of 3R isomer and 1.58 g (48%) of the desired compound as a white solid. ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H), 1.84 (m, 1H), 2.21 (ddd, 1H), 2.82–2.99 (m, 3H), 3.07 (dd, 1H), 3.43 (dd, 1H), 3.97 (br q, 1H), 4.36 (ddd, 1H), 4.55 (br d, 1H), 7.21–7.33 (m, 5H), 7.63 (s, 1H), 8.69 (s, 1H). Mass spectrum: $(M+H)^+$=403.

E. (2S,4S,5S)-4-(tert-Butyldimethylsilyloxy)-5-(tert-butyloxycarbonylamimo)-6-phenyl-2-((5-thiazolyl)-methyl)hexanoic acid

A solution of 1.50 g (3.73 mmol) of the resultant compound of Example 8D in 80 ml of a 2:1 mixture of 1,2-dimethoxyethane and water was treated with 14.9 ml (14.9 mmol) of 1M aqueous lithium hydroxide. After being stirred at ambient temperature for 1.5 h, the bulk of the 1,2-dimethoxyethane was removed in vacuo. The remaining mixture was treated with 10% citric acid to pH 4–5 and extracted with four 50 ml portions of dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give 1.48 g of the crude hydroxy acid. This hydroxy acid was dissolved in 14 ml of dry DMF and

α-isocyanato-L-valine methyl ester, and 100 mg of 4-dimethylaminopyridine in 30 ml of dichloromethane was heated at reflux for 3 h. The resulting solution was allowed to cool, diluted with dichloromethane, washed sequentially with 10% citric acid, aqueous Na_2CO_3, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography using 2% methanol in chloroform to provide 0.95 g (95%) of the desired compound, R_f 0.42 (4% methanol in chloroform). ^1H NMR ($CDCl_3$) δ 0.84 (d, J=7 Hz, 3H), 0.93 (d, J=7Hz, 3H), 2.12 (m, 1H), 3.11 (s, 6H), 3.73 (s, 31H), 4.24 (dd, J=8,4Hz, 1 H), 4.99 (s, 2H), 5.26 (br d, 1H), 6.49 (s, 1H). Mass spectrum: $(M+H)^+$=316.

D. N-((2-(N,N-Dimethylamino)-4-thiazolylmethoxycarbonyl)valine

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 9C provided the desired compound. Mass spectrum: $(M+H)^+$=302.

E. (2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino) carbonyl)-L-valine with the resultant compound of Example 9D provided, after silica gel chromatography using 2% methanol in chloroform, 100 mg of the desired compound (R_f 0.49, 10% methanol in chloroform), mp. 162°–165° C. Mass spectrum: $(M+H)^+$=709.

EXAMPLE 10

(2S,3S,5S)-2-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino) carbonyl)-L-valine with the resultant compound of Example 9D and replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-2-amino-5-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 2% methanol in chloroform, 25 mg (10%) of the desired compound (R_f 0.49, 10% methanol in chloroform), mp. 157–1590C. Mass spectrum: $(M+H)^+$=709.

EXAMPLE 11

A. 4-((Amino)thiocarbonyl)morpholine

A solution of 3.35 g (18.8 mmol) of thiocarbonyl diimidazole in 100 ml of THF was treated with 0.82 ml (9.4 mmol) of morpholine. After being stirred at ambient temperature for 3.5 h, an additional 0.82 ml portion of morpholine was added, and stirring was continued. After 6 h, the solution was treated with excess concentrated aqueous ammonia, and stirred overnight. The resulting solution was concentrated in vacuo, taken up in chloroform, separated from the aqueous phase, dried over Na_2SO_4, and concentrated. Purification of the residue by silica gel chromatography using ethyl acetate provided 1.85 g (76%) of the desired compound, R_f 0.17 (10% methanol in chloroform), as a white solid. ^1H NMR ($CDCl_3$) δ 3.76 (m, 4H), 3.83 (m, 4H), 5.75 (br, 2H). Mass spectrum: $(M+H)^+$=147.

B. Ethyl 2-(4-Morpholinyl)thiazole-4-carboxylate

A mixture of 1.85 g (12.7 mmol) of 4-((amino) thiocarbonyl)morpholine, 1.59 ml (12.7 mmol) of ethyl bromopyruvate, and excess $MgSO_4$ in 50 ml of acetone was heated at reflux for 2 h. The resulting mixture was allowed to cool, filtered, and concentrated in vacuo. The residue was taken up in chloroform, washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. Silica gel chromatography using 1% methanol in chloroform provided 1.7 g (55%) of the desired compound, R_f 0.70 (ethyl acetate). Mass spectrum: $(M+H)^+$=243.

C. 2-(4-Morpholinyl)-4-(hydroxymethyl)thiazole

A solution of 7.0 ml (7.0 mmol) of lithium aluminum hydride in toluene was diluted with 10 ml of THF, cooled to 0° C., and treated with a solution of 1.7 g (7.0 mmol) of ethyl 2-(4-morpholinyl)thiazole-4-carboxylate in 25 ml of THF. The resulting solution was stirred for 1 h, quenched cautiously with aqueous Rochelle's salts, diluted with chloroform, filtered, dired over Na_2SO_4, and concentrated in vacuo. Silica gel chromatography using 2–4% methanol in chloroform provided 856 mg (61%) of the desired compound, R_f 0.16 (4% methanol in chloroform). ^1H NMR ($CDCl_3$) δ 2.44 (br, 1H), 3.46 (t, J=5 Hz, 4H), 3.81 (t, J=5 Hz, 1H), 4.55 (br s, 2H), 6.45 (s, 1H). Mass spectrum: $(M+H)^+$=200.

D. N-((2-(4-Morpholinyl)-4-thiazolyl) methoxycarbonyl)valine Methyl Ester

Using the procedure of Example 9C but replacing 2-(N, N-dimethylamino)-4-(hydroxymethyl)thiazole with 2-(4-morpholinyl)-4-(hydroxymethyl)thiazole provided, after silica gel chromatography using 1% methanol in chloroform, the desired compound, R_f 0.54 (4% methanol in chloroform), in 65% yield. ^1H NMR ($CDCl_3$) δ 0.97 (d, J=7 Hz, 3H), 1.00 (d, J=7 Hz, 3H), 2.25 (m, 1H), 3.50 (dd, J=5, 4 Hz, 2H), 3.76 (s, 3H), 3.84 (dd, J=5, 4 Hz, 2H), 4.67 (dd, J=9, 5 Hz, 1H), 7.63 (br d, 1H), 8.02 (s, 1H).

E. N-((2-(4-Morpholinyl)-4-thiazolyl) methoxycarbonyl)valine

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 11D provided the desired compound.

F. (2S,3S,5S)-5-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino) carbonyl)-L-valine with the resultant compound of Example 11E provided, after silica gel chromatography using 2% methanol in chloroform, 201 mg (92%) of the desired compound (R_f 0.19, 4% methanol in chloroform), mp. 169°–170° C. Mass spectrum: $(M+H)^+$=751.

EXAMPLE 12

(2S,3S,5S)-2-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl) methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)

C. Mass spectrum: $(M+H)^+$=719. Anal. Calcd for $C_{37}H_{46}N_6O_5S_2.0.5H_2O$: C, 61.05; H, 6.51; N, 11.54. Found: C, 61.08; H, 6.32; N, 11.44.

EXAMPLE 16

A. 2-Isopropylthiazole-4-carboxaldehyde

A solution of ethyl 2-isopropylthiazole-4-carboxylate (1 mmol) in 50 ml of dry dichloromethane was cooled to −78° C. under N_2 atmosphere and treated dropwise with 1.2 mmol of diisobutylaluminum hydride (1.5M in toluene). The resulting solution was stirred for 0.5 h, quenched with aqueous Rochelle salts, extracted with dichloromethane, dried over Na_2SO_4, and concentrated in vacuo to provide the crude desired compound.

B. 4-(1-Hydroxyethyl)-2-isopropylthiazole

A solution of the resultant compound of Example 16A (0.5 mmol) in 25 ml of dry THF was cooled to −20° C. under Ar atmosphere, treated with 0.5 mmol of methylmagnesium chloride (3.0M in THF), stirred for 15 min, and quenched with water. The mixture was extracted with ethyl acetate, dried over Na_2SO_4, and concentrated in vacuo to provide the crude desired compound.

C. N-(1-(2-Isopropyl-4-thiazolyl)ethoxycarbonyl) valine Methyl Ester

Using the procedure of Example 5D but replacing 4-(hydroxymethyl) 2-Isopropylthiazole with 4-(1-hydroxyethyl)-2-isopropylthiazole provided the desired compound.

D. N-(1-(²-Isopropyl-4-thiazolyl)ethoxycarbonyl) valine

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 16C provided the desired compound.

E. (2S,3S,5S)-5-(N-(N-(1-(2-Isopropyl-4-thiazolyl) ethoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino) carbonyl)-L-valine with the resultant compound of Example 16D provided the desired compound.

EXAMPLE 17

A. N-((N-Cyclopropyl-N-((2-isopropyl-4-thiazolyl) methyl)amino)carbonyl)-L-valine Methyl Ester

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with the resultant compound of Example 15A provided, after silica gel chromatography using 1% methanol in chloroform, the desired compound (R_f 0.64, 5% methanol in chloroform) in 91% yield. ^{1}H NMR (DMSO-d_6) δ 0.73 (m, 2H), 0.82 (m, 2H), 0.90 (d, J=7 Hz, 6H), 1.30 (d, J=7 Hz, 6H), 2.10 (octet, J=7 Hz, 1H), 2.62 (m, 1H), 3.23 (heptet, J=7 Hz, 1H), 3.64 (s, 3H), 4.10 (dd, J=9, 6 Hz, 1H), 4.45 (AA', 2H), 6.29 (d, J=9 Hz, 1H), 7.06 (s, 1H). Mass spectrum: $(M+H)^+$=354.

B. N-((N-Cyclopropyl-N-((2-isopropyl-4-thiazolyl) methyl)amino)carbonyl)-L-valine

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 17A provided the desired compound.

C. (2S,3S,5S)-5-(N-(N-((N-Cyclopropyl-N-((2-isopropyl-4-thiazolyl)methylamino)carbonyl)valinyl) amino)-2-(N-((5-thiazolylmethoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino) carbonyl)-L-valine with the resultant compound of Example 17B provided, after silica gel chromatography using 1% methanol in chloroform, 85 mg (48%) of the desired compound (R_f 0.30, 5% methanol in chloroform), mp. 65°–66° C. Mass spectrum: $(M+H)^+$=747. Anal. Calcd for $C_{39}H_{50}N_6O_5S_2$: C, 62.71; H, 6.75; N, 11.25. Found: C, 62.74; H, 6.61; N, 11.03.

EXAMPLE 18

A. 4-Chloromethyl-4-hydroxy-2-isopropyloxazoline

To a solution of isobutyramide (9.876 g, 0.1122 mol) in acetone (130 mL) was added 1,3-dichloroacetone (10.0 g, 0.0748 mol), $NaHCO_3$ (9.429 g, 0.1122 mol), and $MgSO_4$ (18.01 g, 0.1496 mol). The mixture was heated at reflux under argon for 63 hrs, then cooled to room temperature, vacuum filtered, and concentrated in vacuo to a dark brown semi-solid. The residue was purified by SiO_2 flash chromatography using a gradient of EtOAc/CH_2Cl_2 (5%, 10%, 20%, 40%) to obtain the desired product as an orange liquid (6.06 g, 0.0341 mol, 46%): ^{1}H NMR ($CDCl_3$) δ 1.20–1.28 (m, 6H), 2.56–2.72 (m, 1H), 3.70 (s, 2H), 4.18 (d, J=9.6 Hz, 1H), 4.38 (d, J=9.6 Hz, 1H). Mass spectrum: $(M+H)^+$=178, 180.

B. 4-Chloromethyl-2-isopropyloxazole

A solution of 4-chloromethyl-4-hydroxy-2-isopropyloxazoline (4.88 g, 0.0275 mol) in 1,2-dichloroethane (20 mL) was added to a solution of $SOCl_2$ (2.40 mL, 0.0329 mol) in 1,2-dichloroethane (80 mL) at 0° C. under argon, and the solution was heated to 70° C. After 15 min at 70° C., the reaction was cooled to room temperature and the solvent removed by rotary evaporation in vacuo. Drying the residue on high vacuum gave the desired compound as a brown semi-solid (4.20 g, 0.0263 mol, 96%): ^{1}H NMR ($CDCl_3$) δ 1.36 (d, J=7.5 Hz, 6H), 3.03–3.18 (m, 1H), 4.50 (s, 2H), 7.56 (s, 1H). Mass spectrum: $(M+H)^+$=160, 162.

C. 2-Isopropyl-4-(((N-methyl)amino)methyl)oxazole

To 40% aqueous methylamine (100 mL) was added dropwise a suspension of 4-chloromethyl-2-isopropyloxazole (4.20 g, 0.0263 mol) in p-dioxane/H_2O (1:1 (v/v), 20 mL) over a 25 min period. After stirring for 45 min at ambient temperature, the volume was reduced to ca. 50 mL by rotary evaporation in vacuo, and NaCl was added. The aqueous was extracted with $CHCl_3$ (4×100 mL), and the combined extract was dried over Na_2SO_4 and concentrated in vacuo. The resulting brown liquid was chromatographed on a 200 g SiO_2 flash column with 2% $iPrNH_2$/CH_2Cl_2 followed by a gradient of $iPrNH_2$/MeOH/CH_2Cl_2 (0.5:2:97.5, 0.5:4:95.5). Concentration in vacuo of the product-containing fractions afforded the desired compound as a golden oil (2.89 g, 0.0187 mol, 71%): ^{1}H NMR ($CDCl_3$) δ 1.33 (d, J=6.9 Hz, 6H), 2.46 (s, 3H), 2.99–3.14 (m, 1H), 3.64 (s, 2H), 7.42 (s, 1H). Mass spectrum: $(M+H)^+$=155, $(M+NH_4)^+$=172.

D. N-((N-Methyl-N-((2-isopropyl-4-oxazolyl) methyl)amino)carbonyl)-L-valine Methyl Ester

A solution of N-(((4-nitrophenyl)oxy)carbonyl)-L-valine methyl ester (0.903 g, 0.00305 mol) in anhydrous DMF (6

vacuo and the yellow solid was dried on vacuum pump to provide the crude desired compound.

F. (2S,3S,5S)-2-Amino-5-(N-((5-oxazolyl) methoxycarbonylamino)-1,6-diphenyl-3-hydroxyhexane

A solution of crude ((5-oxazolyl)methyl)-(4-nitrophenyl) carbonate (made from 0.0132 mol 5-(hydroxymethyl) oxazole) in THF (110 mL) under argon was treated with a solution of (2S,3S,5S)-2,5-diamino-1,6-diphenyl-3-hydroxyhexane (3.76 g, 0.0132 mol) in THF (20 mL), and the reaction stirred at room temperature for 16 hrs. Solvent was removed by rotary evaporation in vacuo and the yellow foam dried on a vacuum pump. Chromatography on a 200 g SiO_2 flash column with 5% MeOH/CH_2Cl_2, 2% $iPrNH_2$/CH_2Cl_2, and a gradient of $iPrNH_2$/MeOH/CH_2Cl_2 (2:2:96, 2:5:93) afforded a mixture (1.74 g) of the desired compound and (2S,3S,5S)-5-amino-2-(N-((5-oxazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane. The mixture was applied to a 150 g SiO_2 flash column (deactivated with 2% $iPrNH_2/CH_2Cl_2$) and eluted with 2% $iPrNH_2/CH_2Cl_2$ to afford the desired compound as a gummy light yellow solid (0.382 g, 0.933 mmol, 7%): ^1H NMR (DMSO-d_6) δ 1.16–1.30 (m, 1H), 1.36–1.47 (m, 1H), 2.56–2.66 (m, 2H), 2.75–2.85 (m, 1H), 2.89–3.01 (m, 1H), 3.53–3.71 (m, 3H), 4.97 (d, J=2.4 Hz, 2H), 7.01 (d, J=9 Hz, 1H), 7.11–7.32 (m, 14H), 8.36 (s, 1H). Mass spectrum: $(M+H)^+$=410.

G. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U but replacing (2S, 3S,5S)-5-amino-2-(N-((5-thiazolyl)-methoxycarbonyl) amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane and replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-isopropyl-4-oxazolyl)methyl) amino)carbonyl)-L-valine provided, after silica gel chromatography using a gradient of 1%–4% methanol in dichloromethane, 145 mg (80%) of the desired compound. ^1H NMR ($CDCl_3$) δ 0.74 (d, J=6.9 Hz, 6H), 1.23 (d, J=6.9 Hz, 6H), 1.39–1.50 (m, 2H), 1.80–1.94 (m, 1H), 2.56–2.74 (m, 4H), 2.83 (s, 3H), 2.94–3.09 (m, 1H), 3.52–3.62 (m, 1H), 3.72–3.84 (m, 1H), 3.88–3.92 (m, 1H), 4.08–4.35 (m, 3H), 4.62 (d, J=6Hz, 1H), 4.94 (s, 2H), 5.91 (d, J=8.4 Hz, 1H), 6.89 (d, J=9 Hz, 1H), 7.06–7.26 (m, 11H), 7.69 (d, J=9 Hz, 1H), 7.77 (s, 1H), 8.35 (s, 1H). Mass spectrum: $(M+NH_4)^+$=706; $(M+H)^+$=689. Anal. Calcd for $C_{37}H_{48}N_6O_7.0.5\ H_2O$: C, 63.68; H, 7.08; N, 12.04. Found: C, 63.50; H, 7.13; N, 11.60.

EXAMPLE 20

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U but replacing (2S, 3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl) amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 1% methanol in chloroform, 88 mg (55%) of the desired compound (R_f 0.4, 5% methanol in chloroform), mp. 59°–61° C. Mass spectrum: $(M+H)^+$=705. Anal. Calcd for $C_{37}H_{48}N_6O_6S.0.5H_2O$: C, 62.25; H, 6.92; N, 11.77. Found: C, 62.23; H, 6.55; N, 11.57.

EXAMPLE 21

A. Methyl 4-isopropylthiazole-2-carboxylate

A mixture of 2.11 g (12.8 mmol) of 1-bromo-3-methylbutan-2-one (Gaudry and Marquet, Tetrahedron, 26, 5661 (1970)), 1.0 g (12.8 mmol) of ethyl thiooxamate, and 1.70 g (14 mmol) of $MgSO_4$ in 50 ml of acetone was heated at reflux for 3 h. After being allowed to cool, the mixture was filtered, concentrated in vacuo, and purified by silica gel chromatography using chloroform to provide 0.29 g (11%) of the desired compound (R_f 0.9, 4% methanol in chloroform). ^1H NMR (DMSO-d_6) δ 1.27 (d, J=7 Hz, 6H), 1.32 (t, J=7Hz, 3H), 3.12 (heptet, J=7Hz, 1H), 4.37 (q, J=7Hz, 2H), 7.73 (s, 1H). Mass spectrum: $(M+H)^+$=200.

B. 2-(Hydroxymethyl)-4-isopropylthiazole

Using the procedure of Example 5B, but replacing ethyl 2-isopropyl-4-thiazolecarboxylate with methyl 4-isopropylthiazole-2-carboxylate provided, after silica gel chromatography using 2% methanol in chloroform, the desired compound (R_f 0.3, 5% methanol in chloroform) in 96% yield.

C. N-((4-Isopropyl-2-thiazolyl)methoxycarbonyl) valine Methyl Ester

A solution of 1.4 mmol of α-isocyanato-valine methyl ester and 0.22 g (1.4 mmol) of 2-(hydroxymethyl)-4-isopropylthiazole in 10 ml of chloroform was heated at reflux for 3 h. After being allowed to cool, the solvent was removed in vacuo, and the residue was purified by silica gel chromatography using 2% methanol in chloroform to provide 0.23 g (52%) of the desired compound (R_f 0.54, 5% methanol in dichloromethane). NMR ^1H NMR (DMSO-d_6) δ 0.87 (d, J=7 Hz, 3H), 0.88 (d, J=7 Hz, 3H), 1.23 (d, J=7 Hz, 6H), 2.04 (octet, J=7 Hz, 1H), 3.01 (heptet, J=7 Hz, 1H), 3.73 (s, 3 H), 3.94 (dd, J=8, 6 Hz, 1H), 5.26 (AA', 2H), 7.28 (s, 1H), 7.92 (d, J=8 Hz, 1H). Mass spectrum: $(M+H)^+$=315.

D. N-((4-Isopropyl-2-thiazolyl)methoxycarbonyl) valine

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 21C provided the desired compound.

E. (2S,3S,5S)-5-(N-(N-((4-Isopropyl-2-thiazolyl) methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolylmethoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino) carbonyl)-L-valine with the resultant compound of Example 21D provided, after silica gel chromatography using 1% methanol in chloroform, 123 mg (61%) of the desired compound (R_f 0.4, 5% methanol in chloroform), mp. 62°–64° C. Mass spectrum: $(M+H)^+$=708.

EXAMPLE 22

A. N,N-Diethylthiourea

A mixture of 6.24 g (35 mmol) of thiocarbonyl diimidazole and 3.6 ml (35 mmol) of diethylamine in 50 ml of THF

chromatography using 3% methanol in chloroform, the desired compound, R_f 0.3, (5% methanol in chloroform) in 25% yield. ^1H NMR (d_6-DMSO) δ 1.30 (d, J=7 Hz, 6H), 3.22 (heptet, J=7 Hz, 1H), 4.61 (dd, J=6, 1 Hz, 2H), 5.45 (t, J=6 Hz, 1H), 7.48 (br s, 1H).

C. N-((2-Isopropyl-5-thiazolyl)methoxycarbonyl) valine Methyl Ester

Using the procedure of Example 5D but replacing 4-(hydroxymethyl)-2-isopropylthiazole with 5-(hydroxymethyl)-2-isopropylthiazole provided, after silica gel chromatography using 3% methanol in chloroform, the desired compound, R_f 0.8, (5% methanol in chloroform) in 29% yield. ^1H NMR δ 0.89 (d, J=7 Hz, 6H), 0.95 (d, J=7 Hz, 3H), 0.97 (d, J=7 Hz, 3H) 2.14 (m, 1H), 3.33 (heptet, J=7 Hz, 1H), 3.74 (s, 3H), 4.30 (dd, J=9, 5 Hz, 1H), 5.23 (s, 2H), 5.25 (br d, 1H), 7.63 (s, 1H). Mass spectrum: $(M+H)^+$=315.

D. N-((2-Isopropyl-5-thiazolyl)methoxycarbonyl) valine

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 24C provided the desired compound.

E. (2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl) methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino) carbonyl)-L-valine with the resultant compound of Example 24D provided the desired compound.

EXAMPLE 25

A. 2-Methoxythioacetamide

Using the procedure of Example 1O but replacing isobutyramide with 2-methoxyacetamide provided the desired compound in 52% yield.

B. 4-(Chloromethyl)-2-(methoxymethyl)thiazole hydrochloride

Using the procedure of Example 1P but replacing 2-methylpropane thioamide with 2-methoxythioacetamide provided the crude desired compound in 41% yield.

C. 2-(Methoxymethyl)-4-(((N-methyl)amino) methyl)thiazole

Using the procedure of Example 1Q but replacing 4-(chloromethyl)-2-isopropylthiazole hydrochloride with 4-(chloromethyl)-2-(methoxymethyl) thiazole hydrochloride provided, after silica gel chromatography using 3% methanol in chloroform, the desired compound, R_f 0.1, (5% methanol in chloroform) in 73% yield.

D. N-((N-Methyl-N-((2-(methoxymethyl)-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester

Using the procedure of Example 1S but replacing 2-isopropyl-4-(((N-methyl)amino)-methyl)thiazole with 2-(methoxymethyl)-4-(((N-methyl)amino)-methyl)thiazole provided, after silica gel chromatography using 3% methanol in chloroform, the desired compound, R_f 0.5, (5% methanol in chloroform) in 23% yield.

E. N-((N-Methyl-N-((2-(methoxymethyl)-4-thiazolyl)methyl)amino)carbonyl)-L-valine

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 25D provided the desired compound.

F. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(methoxymethyl)-4-thiazolyl)methyl)amino) carbonyl)valinyl)amino)-2-(N-((5-thiazolylmethoxycarbonylamino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino) carbonyl)-L-valine with the resultant compound of Example 25E provided the desired compound.

EXAMPLE 26

A. 1,1-Diethoxy-4-((3,4,5,6-tetrahydro-2H-1pyran-2-yl)oxy)-2-butyne

A 1M solution of ethylmagnesium bromide in THF (200 ml, 0.2 mol) was treated with 29 ml (0.2 mol) of a solution of 3,4,5,6-tetrahydro-2-(2-propynyloxy)-2H-pyran in toluene, while maintaining ambient temperature through use of a cool water bath. The resulting solution was stirred for 4 h and treated with 47 ml (0.28 mol) of a solution of triethylorthoformate in toluene, while maintaining ambient temperature with a cool water bath. The resulting solution was heated to 85° C. for 8 h, allowing the removal of THF by distillation. After being allowed to cool, the resulting solution was poured into 500 ml of ice-water containing 29 g of NH_4OAc, extracted with two portions of ether, dried over K_2CO_3, and concentrated in vacuo. The residue was distilled at ca. 0.5 mm Hg pressure (b.p. 103°–108° C.) to provide 39.5 g (79%) of the desired compound. ^1H NMR ($CDCl_3$) 61.24 (t, J=7 Hz, 6H), 1.5–1.9 (m, 6H), 3.5–3.65 (m, 3H), 3.7–3.9 (m, 3H), 4.32 (AA', 2H), 4.81 (m, 1H), 5.31 (m, 1H). Mass spectrum: $(M+NH_4)^+$=260.

B. 5-(Hydroxymethyl)isoxazole

A solution of 39.28 g (161 mmol) of the resultant compound of Example 26A and 26 g (376 mmol) of hydroxylamine hydrochloride in 168 ml of ethanol and 34 ml of water was heated at reflux under N_2 atmosphere for 1 h. After being allowed to cool, the resulting solution was concentrated in vacuo to ⅓ the original volume, diluted with 50 ml of water, and extracted with 2 portions, of ether. The combined extracts were concentrated to an oil. The crude product (7.04 g, 44%) was obtained after distillation (79°–84° C., 0.5 mm Hg). Silica gel chromatography using 0–3% methanol in dichloromethane provided 4.9 g of the desired compound contaminated with 5-hydroxypentanal oxime. ^1H NMR ($CDCl_3$) δ 1.95 (br, 1H), 4.81 (s, 2H), 6.27 (d, J=1 Hz, 1H), 8.23 (d, J=1 Hz, 1H). Mass spectrum: $(M+NH_4)^+$=117.

C. ((5-Isoxazolyl)methyl)-(4-nitrophenyl)carbonate

Using the procedure of Example 1L, but replacing 5-(hydroxymethyl) thiazole with 5-(hydroxymethyl) isoxazole provided, after silica gel chromatography using 8:2 dichloromethane:hexane, the desired compound. ^1H NMR ($CDCl_3$) δ 5.41 (s, 2H), 6.46 (d, J=1 Hz, 1H), 7.40 (m, 2H), 8.30 (m, 3H). Mass spectrum: $(M+NH_4)^+$=282.

D. (2S,3S,5S)-5-Amino-2-(N-((5-isoxazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

A mixture of 1.54 g (5.41 mmol) of (2S,3S,5S)-2,5-diamino-1,6-diphenyl-3-hydroxyhexane and 0.673 g (5.41

B. 5-(Hydroxymethyl)-3-isopropylisoxazole

Using the procedure of Example 26B but replacing the resultant compound of Example 26A with the resultant compound of Example 29A provided the desired compound.

C. N-((3-Isopropyl-5-isoxazolyl)methoxycarbonyl) valine Methyl Ester

Using the procedure of Example 5D but replacing 4-(hydroxymethyl)-2-isopropylthiazole with 5-(hydroxymethyl)-3-isopropylisoxazole provided the desired compound.

D. N-((3-Isopropyl-5-isoxazolyl)methoxycarbonyl) valine

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 29C provided the desired compound.

E. (2S,3S,5S)-5-(N-(N-((3-Isopropyl-5-isoxazolyl) methoxycarbonyl)valinylamino)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino) carbonyl)-L-valine with the resultant compound of Example 29D provided the desired compound.

EXAMPLE 30

A. 2-Isopropyl-4-(methanesulfonyloxymethyl) thiazole

A solution of 1.2 mmol of 4-(hydroxymethyl)-2-isopropylthiazole and 1.3 mmol of diisopropylethylamine in 20 ml of dichloromethane was cooled to −20° C. and treated dropwise with 1.3 mmol of methanesulfonyl chloride. The resulting mixture was stirred for 1 h, quenched with aqueous citric acid, separated, dried over Na_2SO_4, and concentrated in vacuo to provide the desired compound.

B. 2-Isopropyl-4-(mercaptomethyl)thiazole

A mixture of 0.8 mmol of the resultant compound of Example 30A and 1.0 mmol of sodium hydrosulfide hydrate in 20 ml of THF was heated at reflux until analysis by thin layer chromatography indicated consumption of starting material. The resulting mixture was allowed to cool, concentrated in vacuo, partitioned between dichloromethane and water, dried over Na_2SO_4, and concentrated to provide the crude desired compound.

C. N-((2-Isopropyl-4-thiazolyl) thiomethoxycarbonyl)valine Methyl Ester.

Using the procedure of Example 5D, but replacing 4-(hydroxymethyl)-2-isopropylthiazole with the resultant compound of Example 30B provided, after chromatography on silica gel, the desired compound.

D. N-((2-Isopropyl-4-thiazolyl)thiomethoxycarbonyl) valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 30C provided the desired compound.

E. (2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl) thiomethoxycarbonyl)valinylamino)-2-(N-((5-thiazolylmethoxycarbonylamino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino) carbonyl)-L-valine with the resultant compound of Example 30D provided, after purification by silica gel chromatography, the desired compound.

EXAMPLE 31

A. 2-Isopropylthiazole-4-carboxaldehyde

A solution of 3.1 g (15.6 mmol) of ethyl 2-isopropylthiazole-4-carboxylate in 50 ml of dichloromethane was cooled under N_2 atmosphere to −78° C. and treated dropwise with 15.6 ml (23.4 mmol) of a 1.5M solution of diisobutylaluminum hydride in toluene over a period of 1.5 h. After being stirred for an additional 0.5 h, the solution was quenched with 5 ml of methanol followed by 15 ml of aqueous Rochelle's salt. The resulting mixture was partitioned between chloroform and aqueous Rochelle's salt, dried over Na_2SO_4, and concentrated to provide 1.37 g (56%) of the crude desired compound, R_f 0.47 (20% ethyl acetate in hexane). ^1H NMR ($CDCl_3$) δ 1.45 (d, J=7 Hz, 6H), 3.39 (heptet, J=7 Hz, 1H), 8.07 (s, 1H), 10.00 (s, 1H). Mass spectrum: $(M+H)^+$=156.

B. (E)-Ethyl 3-(2-Isopropyl-4-thiazolyl)propenoate

A slurry of 60% NaH (18 mmol) in mineral oil was washed with hexane, decante under N_2 atmosphere, and diluted with 25 ml of THF. The resulting mixture was cooled to 0° C., treated portionwise with 3.24 ml (16.4 mmol) of triethylphosphonoacetate. After addition, the solution was stirred for 10 min, treated with 1.37 g (8.84 mmol) of 2-isopropylthiazole-4-carboxaldehyde in 25 ml of THF, allowed to warm to ambient temperature for 25 min, and quenched with 100 ml of saturated aqueous NH_4Cl. The mixture was extracted with three 100 ml portions of ethyl acetate, dried over Na_2SO_4, and concentrated in vacuo. Silica gel chromatography of the residue using 5–10% ethyl acetate in hexane provided 1.61 g (81%) of the desired compound, R_f 0.64 (20% ethyl acetate in hexane). ^1H NMR ($CDCl_3$) δ 1.33 (t, J=7Hz, 3H), 1.42 (d, J=7Hz, 6H), 3.32 (heptet, J=7 Hz, 1H), 4.26 (q, J=7 Hz, 2H), 6.75 (d, J=15 Hz, 1H), 7.29 (s, 1H), 7.57 (d, J=15 Hz, 1H).

C. Methyl 3-(2-Isopropyl-4-thiazolyl)propanoate

A solution of 225 mg (1 mmol) of (E)-ethyl 3-(2-isopropyl-4-thiazolyl) propenoate in 10 ml of freshly distilled (from calcium hydride) methanol and 1 ml of dry THF was treated with 49 mg (2 mmol) of magnesium turnings. The mixture was stirred for 20 min, during which the magnesium was consumed. The resulting solution was poured over cold aqueous HCl, basified to pH 8 with $NaHCO_3$, extracted with ethyl acetate, dried over Na_2SO_4, and concentrated. Silica gel chromatography using 10% ethyl acetate in hexane provided a mixture of the desired compound and methyl 3-(2-isopropyl-4-thiazolinyl) propanoate.

D. 3-(2-Isopropyl-4-thiazolyl)propanoic Acid

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 31C provided the desired compound.

E. (2S,3S,5S)-5-(N-(N-(tert-Butyloxycarbonyl) valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl) amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)

2H), 3.60 (dt, J=11, 4 Hz, 2H), 3.92 (d, J=3 Hz, 2H), 7.2–7.4 (m, 10H). Mass spectrum: $(M+H)^+$=301.

B. (2S,3S,4S,5S)-2-Amino-5-(N-((5-thiazolyl) methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane

Using the procedure of Example 1M but replacing (2S, 3S,5S)-2,5-diamino-1,6-diphenyl-3-hydroxyhexane with (2S,3S,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane provided, after silica gel chromatography, the desired compound.

C. (2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)aminocarbonyl)valinyl) amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane

Using the procedure of Example 1U but replacing (2S, 3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl) amino)-1,6-diphenyl-3-hydroxyhexane with the resultant compound of Example 35B provided, after purification by silica gel chromatography, the desired compound.

EXAMPLE 36

A. (4S,5S,1'R,2'S)-5-(1-Acetoxy-2-(N-((((benzyl oxycarbonyl)amino)-3-phenylpropyl)-4-benzyl-oxazolidin-2-one

A suspension of 5.02 g (8.80 mmol) of (2S,3R,4R,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane in 400 ml of acetonitrile was treated dropwise with 3 ml (20 mmol) of α-acetoxyisobutyryl bromide. The resulting solution was stirred under N_2 atmosphere at ambient temperature for 2 h, filtered to remove traces of solid starting material, quenched cautiously with 100 ml of aqueous $NaHCO_3$, and concentrated in vacuo to a volume of 100 ml. The resulting mixture was extracted with two 100 ml portions of dichloromethane, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography using first 10% then 25% ethyl acetate in dichloromethane to provide 3.15 g (71%) of the desired compound as a white foam. ^1H NMR ($CDCl_3$) δ 2.09 (s, 3H), 2.53 (br t, J=12 Hz, 1H), 2.72 (dd, J=13, 3 Hz, 1H), 2.83 (dd, J=14,8 Hz, 1H), 2.95 (dd, J=14,7 Hz, 1H), 3.95 (m, 1H), 4.45 (m, 1H), 4.8 (m, 2H), 5.0–5.1 (m, 3H), 5.29 (dd, J=9, 3 Hz, 1H), 7.0–7.4 (m, 10H). Mass spectrum: $(M+NH_4)^+$=520.

B. (2S,3R,4S,5S)-2,5-Diamino-3,4-dihydroxy-1,6-diphenylhexane

Using the procedure of Example 1F but replacing the resultant compound of Example 1E with (4S,5S,1'R,2'S)-5-(1-acetoxy-2-(N-(benzyloxycarbonylamino))-3-phenylpropyl)-4-benzyl-oxazolidin-2-one provided the desired compound mixed with benzyl alcohol. Purification of a small portion by silica gel chromatography using 5% methanol/2% isopropylamine in chloroform provided the pure desired compound., m.p. 115°–119° C. ^1H NMR ($CDCl_3$) δ 2.46 (dd, J=14, 9 Hz, 1H), 2.61 (dd, J=14, 11 Hz, 1H), 3.02 (td, J=9, 3 Hz, 1H), 3.19 (dd, J=14,4 Hz, 1H), 3.35–3.4 (m, 2H), 3.51 (t, J=9 Hz, 1H), 3.76 (dd, J=9, 3 Hz, 1H), 7.2–7.4 (m, 10H).

C. (2S,3R,4S,5S)-5-Amino-2-(N-((5-thiazolyl) methoxycarbonylamino)-3,4-dihydroxy-1,6-diphenylhexane

A solution of 0.133 mmol of (2S,3R,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane and 0.147 mmol of ((5-thiazolyl)methyl)-(4-nitrophenyl)-carbonate in 10 ml of tetrahydrofuran was stirred at ambient temperature for 16 h. The resulting solution was diluted with 50 ml of chloroform, washed with several portions of 3N aqueous NaOH, dried over Na_2SO_4, and concentrated in vacuo. Silica gel chromatography of the residue provided the desired compound.

D. (2S,3R,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl) valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl) amino)-3,4-dihydroxy-1,6-diphenylhexane

Using the procedure of Example 1U but replacing (2S, 3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl) amino)-1,6-diphenyl-3-hydroxyhexane with the resultant compound of Example 36C provided, after purification by silica gel chromatography, the desired compound.

EXAMPLE 37

A. (2S,3R,4S,5S)-2-Amino-5-(N-((5-thiazolyl) methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane

Using the procedure of Example 1U but replacing (2S, 3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl) amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3R,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane provided, after purification by silica gel chromatography, the desired compound.

B. (2S,3R,4S,5S)-2-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl) valinyl)amino)-5-(N-5-thiazolyl)methoxycarbonyl) amino)-3,4-dihydroxy-1,6-diphenylhexane

Using the procedure of Example 36C but replacing (2S, 3R,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane with the resultant compound of Example 37A provided, after purification by silica gel chromatography, the desired compound.

EXAMPLE 38

A. 5-(Hydroxymethyl)-3-isopropylisothiazole

The desired compound was prepared from the resultant compound of Example 29A using the procedure of Lucchesini, et. al. (Heterocycles, 29, 97 (1989)).

B. N-((3-Isopropyl-5-isothiazolyl)methoxycarbonyl) valine Methyl Ester

Using the procedure of Example 5D but replacing 4-(hydroxymethyl)-2-isopropylthiazole with 5-(hydroxymethyl)-3-isopropylisothiazole provided the desired compound.

C. N-((3-Isopropyl-5-isothiazolylmethoxycarbonyl) valine

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 38B provided the desired compound.

D. (2S,3S,5S)-5-(N-(N-((3-Isopropyl-5-isothiazolyl) methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)

(2S,3R,4R,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl) methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino) carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclohexyl-4-thiazolyl)methyl)amino) carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,1-dimethyl)ethyl-4-thiazolyl)methyl) amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclobutyl-4-thiazolyl)methyl)amino) carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopropyl-4-thiazolyl)methyl)amino) carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethyl-4-thiazolyl)methyl)amino) carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethenyl-4-thiazolyl)methyl)amino) carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclopentenyl)-4-thiazolyl) methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclohexenyl)-4-thiazolyl)methyl) amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclopentenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclohexenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl-1-propenyl)-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl-1-propenyl)-4-thiazolyl) methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl) amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1 ,2-dimethyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclopentyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclohexyl)methyl-4-thiazolyl)methyl) amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-phenyl-4-thiazolyl)methyl)amino) carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-benzyl-4-thiazolyl)methyl)amino) carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl)ethyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-phenyl-4-thiazolyl)methyl)amino) carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-benzyl-4-thiazolyl)methyl)amino) carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl)ethyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl-1-ethenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(4-fluoro)phenyl-4-thiazolyl)methyl) amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-chloro)phenyl-4-thiazolyl)methyl) amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-methoxy)phenyl-4-thiazolyl)methyl) amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)-4-thiazolyl)methyl)amino) carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)methyl-4-thiazolyl)methyl) amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-methoxy-4-thiazolyl)methyl)amino) carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethoxy-4-thiazolyl)methyl)amino) carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyloxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(N,N-dimethylamino)methyl-4-thiazolyl)-methyl)amino) carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl) methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-pyrrolidinyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-propyl-4-thiazolyl)methyl)amino) carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl)propyl-4-thiazolyl)methyl) amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl)propyl-4-thiazolyl)methyl) amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-ethyl)propyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino) carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclohexyl-4-thiazolyl)methyl)amino) carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,1-dimethyl)ethyl-4-thiazolyl)methyl) amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclobutyl-4-thiazolyl)methyl)amino) carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopropyl-4-thiazolyl)methyl)amino) carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethyl-4-thiazolyl)methyl)amino) carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethenyl-4-thiazolyl)methyl)amino) carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclopentenyl)-4-thiazolyl) methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclohexenyl)-4-thiazolyl)methyl) amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclopentenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclohexenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl-1-propenyl)-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Ethyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((3-Isopropyl-5-isoxazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Ethyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((3-Isopropyl-5-isoxazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

EXAMPLE 41

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedures of Example 18A–F, but replacing isobutyramide with propionamide, provided the desired compound. ^{1}H NMR (DMSO-d_6) δ 0.74 (d, J=6 Hz, 6H), 1.19 (t, J=7 Hz, 3H), 1.38–1.51 (m, 2H), 1.80–1.94 (m, 1H), 2.54–2.74 (m, 5H), 2.83 (s, 3H), 3.53–3.63 (m, 1H), 3.82 (br q, 1H), 3.92 (t, J=8 Hz, 1H), 4.13, (m, 1H), 4.26 (AA', 2H), 4.63 (d, J=6 Hz, 1H), 5.13 (AA', 2H), 5.90 (d, J=9 Hz, 1H), 6.89 (d, J=9 Hz, 1H), 7.07–7.25 (m, 12H), 7.68 (d, J=8.7 Hz, 1H), 7.77 (s, 1H), 7.86 (s, 1H), 9.05 (s, 1H). Mass spectrum: $(M+H)^+$=691. Anal. Calcd for $C_{36}H_{46}N_6O_6S.0.3H_2O$: C, 62.10; H, 6.75; N, 12.07. Found: C, 62.42; H, 6.68; N, 11.69.

EXAMPLE 42

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-methyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedures of Example 18A–F, but replacing isobutyramide with acetamide, provided the desired compound. Mass spectrum: $(M+H)^+$=677.

EXAMPLE 43

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolylmethyl)amino)carbonyl)valinyl)amino)-1-phenyl-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-6-(5-oxazolyl)-3-hydroxyhexane

Using the procedures of Example 8C–8K, but replacing 5-chloromethylthiazole hydrochloride with 5-chloromethyloxazole hydrochloride provided the desired compound.

4-(chloromethyl)-2-(1-pyrrolidinyl)thiazole hydrochloride provided, after purification of the residue by silica gel chromatography using 2% isopropylamine/2% methanol in chloroform, 0.89 g (30%) of the desired compound. ^{1}H NMR ($CDCl_3$) δ 2.02 (m, 4H), 2.61 (s, 3H), 3.44 (m, 4H), 3.90 (s, 2H), 4.84 (br, 1H), 6.51 (s, 1H). Mass spectrum: $(M+H)^+$=198.

D. N-((N-Methyl-N-((2-(1-pyrrolidinyl)-4-thiazolyl) methyl)amino)carbonyl)-L-valine Methyl Ester

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-(1-pyrrolidinyl)-4-(((N-methyl)amino) methyl)thiazole provided, after purification by silica gel chromatography using 4% methanol in chloroform as an eluent, 0.63 g (39%) of the desired compound. ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J=7 Hz, 3H), 0.98 (t, J=7 Hz, 3H), 2.04 (m, 4H), 2.14 (heptet, J=7 Hz, 1H), 2.97 (s, 3H), 3.45 (m, 4H), 3.71 (s, 3H), 4.10 (m, 1H), 4.33 (dd, J=9, 6 Hz, 1H), 4.42 (br d, J=16 Hz, 1H), 6.26 (s, 1H), 6.45 (br, 1H). Mass spectrum: $(M+H)^+$=355.

E. N-((N-Methyl-N-((2-(1-pyrrolidinyl)-4-thiazolyl) methyl)amino)carbonyl)-L-valine

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 46D provided 0.24 g (96%) of the desired compound.

F. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-pyrrolidinyl)-4-thiazolyl)methyl)amino)carbonyl) valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl) amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino) carbonyl)-L-valine with N-((N-methyl-N-((2-(1-pyrrolidinyl)-4-thiazolyl)methyl)amino)carbonyl)-L-valine provided, after purification by silica gel chromatography using 2% methanol in chloroform, the desired compound (R_f 0.29, 4% methanol in chloroform). Mass spectrum: $(M+H)^+$=748.

EXAMPLE 47

A. Ethyl 2-(2-Isopropyl-4-thiazolyl)acetate

Using the procedure of Example 1P, but replacing 1,3-dichloroacetone with ethyl 4-chloroacetoacetate provided, after purification by silica gel chromatography using $CHCl_3$, the desired compound in 34% yield. ^{1}H NMR (d_6-DMSO) δ 1.18 (t, J=7 Hz, 3H), 1.30 (d, J=7 Hz, 6H), 3.24 (heptet, J=7 Hz, 1H), 3.76 (s, 2H), 4.09 (q, J=7 Hz, 2H), 7.31 (s, 1H). Mass spectrum: $(M+H)^+$=214.

B. 4-(2-Hydroxyethyl)-2-isooropylthiazole

Using the procedure of Example 5B, but replacing ethyl 2-isopropyl-4-thiazolecarboxylate with ethyl 2-(2-isopropyl-4-thiazolyl)acetate provided, after purification of the residue by silica gel chromatography using 2% methanol in chloroform, 0.9 g (47%) of the desired compound. ^{1}H NMR ($CDCl_3$) δ 1.40 (d, J=7 Hz, 6H), 2.95 (t, J=6 Hz, 2H), 3.30 (heptet, J=7 Hz, 1H), 3.92 (t, J=6 Hz, 2H), 6.83 (s, 1H). Mass spectrum: $(M+H)^+$=172.

C. N-((2-(2-Isopropyl-4-thiazolyl)ethoxy)carbonyl) valine Methyl Ester

Using the procedure of Example 5D, but replacing 4-(hydroxymethyl)-2-isopropylthiazole with 4-(2-hydroxyethyl)-2-isopropylthiazole provided, after purification by silica gel chromatography using 3% methanol in chloroform as an eluent, 0.8 g (52%) of the desired compound.

D. N-((2-(2-Isopropyl-4-thiazolyl)ethoxy)carbonyl) valine

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 47C provided 0.17 g (82%) of the desired compound.

E. (2S,3S,5S)-5-(N-(N-((2-(2-Isopropyl-4-thiazolyl) ethoxy)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino) carbonyl)-L-valine with N-((2-(2-isopropyl-4-thiazolyl) ethoxy)carbonyl)valine provided, after purification by silica gel chromatography using 99:1 $CHCl_3$:CH_3OH, 80 mg (47%) of the desired compound (R_f 0.3, 95:5 $CHCl_3$:CH_3OH) as a solid, mp 146°–147° C. Mass spectrum: $(M+H)^+$=722. Anal. Calcd for $C_{37}H_{47}N_5O_6S_2$: C, 61.56; H, 6.56; N, 9.70. Found: C, 61.24; H, 6.48; N, 9.53.

EXAMPLE 48

E. (2S,3S,5S)-2-(N-(N-((2-(2-Isopropyl-4-thiazolyl) ethoxy)carbonyl)valinyl)amino)-5-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino) carbonyl)-L-valine with N-((2-(2-isopropyl-4-thiazolyl) ethoxy)carbonyl)valine and replacing (2S,3S,5S)- 5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-2-amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after purification by silica gel chromatography using 99:1 $CHCl_3$:CH_3OH, 50 mg (30%) of the desired compound (R_f 0.3, 95:5 $CHCl_3$:CH_3OH) as a solid, mp 159°–160° C. Mass spectrum: $(M+H)^+$=722 HRMS. Exact mass calcd for $C_{37}H_{47}N_5O_6S_2$: 722.3046. Found: 722.3036.

EXAMPLE 49

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-pyrrolidinyl)-4-thiazolyl)methyl)amino)carbonyl) valinyl)amino)-2-(N-((5-isoxazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino) carbonyl)-L-valine with N-((N-methyl-N-((2-(1-pyrrolidinyl)-4-thiazolyl)methyl)amino)carbonyl)-L-valine and replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-2-(N-((5-isoxazolyl)methoxy-carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after purification by silica gel chromatography using 2% methanol in chloroform, the desired compound (R_f 0.30, 4% methanol in chloroform).

EXAMPLE 50

A. (2S,3S,5S)-5-(N-(N-(t-Butyloxycarbonyl)valinyl) amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)

G. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclobutyl-4-thiazolyl)methyl)amino)carbonyl) valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl) amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino) carbonyl)-L-valine with N-((N-methyl-N-((2-cyclobutyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine provided, after purification by silica gel chromatography using 1% methanol in chloroform, 110 mg (64%) of the desired compound (R_f 0.17, 95:5 CH_2Cl_2:CH_3OH) as a solid, mp 74°–76° C. Mass spectrum: $(M+H)^+$=733. Anal. Calcd for $C_{38}H_{48}N_6O_5S_2$: C, 62.27; H, 6.60; N, 11.47; S, 8.75. Found, C, 62.02; H, 6.73; N, 11.33; S, 8.51.

EXAMPLE 53

A. Propanethioamide

Using the procedure of Example 10, but replacing isobutyramide with propionamide provided 4.6 g (38%) of the crude desired compound. ^1H NMR ($CDCl_3$) δ 1.33 (t, J=7 Hz, 3H), 2.70 (q, J=7 Hz, 2H), 6.9 (br, 1H), 7.6 (br, 1H). Mass spectrum: $(M+H)^+$=90.

B. 4-(Chloromethyl)-2-ethylthiazole hydrochloride

Using the procedure of Example 1P, but replacing 2-methylpropane thioamide with propanethioamide provided the crude desired compound as a yellow oil.

C. 2-Ethyl-4-(((N-methyl)amino)methyl)thiazole

Using the procedure of Example 1Q, but replacing 4-(chloromethyl)2-isopropylthiazole hydrochloride with 4-(chloromethyl)-2-ethylthiazole hydrochloride provided 1.0 g (52%) of the desired compound.

D. N-((N-Methyl-N-((2-ethyl-4-thiazolyl)methyl) amino)carbonyl)-L-valine Methyl Ester

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-ethyl-4-(((N-methyl)amino)methyl)thiazole provided, after purification by silica gel chromatography using 1% methanol in chloroform as an eluent, 0.7 g (35%) of the desired compound.

E. N-((N-Methyl-N-((2-ethyl-4-thiazolyl)methyl) amino)carbonyl)-L-valine

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 53D provided 0.28 g (43%) of the desired compound.

F. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino) carbonyl)-L-valine with N-((N-methyl-N-((2-ethyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine provided, after purification by silica gel chromatography using 1% methanol in chloroform, 60 mg (40%) of the desired compound (R_f 0.14, 95:5 CH_2Cl_2:CH_3OH) as a solid, mp 70°–71° C. Mass spectrum: $(M+H)^+$=707. Anal. Calcd for $C_{36}H_{46}N_6O_5S_2.H_2O$: C, 59.65; H, 6.67; N, 11.59. Found: C, 59.64; H, 6.59; N, 11.88.

EXAMPLE 54

A. 2-Isopropyl-4-(((N-(1-propyl))amino)methyl) thiazole

Using the procedure of Example 1Q, but replacing 40% aqueous methylamine with 1-aminopropane provided the crude desired compound. ^1H NMR ($CDCl_3$) δ 0.94 (t, J=7 Hz, 3H), 1.39 (d, J=7 Hz, 6H), 1.54 (sextet, J=7 Hz, 2H), 2.62 (t, J=7 Hz, 2H), 3.30 (heptet, J=7 Hz, 1H), 3.87 (d, J=1 Hz, 2H), 6.93 (s,1H). Mass spectrum: $(M+H)^+$=199.

B. N-((N-(1-Propyl)-N-((2-isopropyl-4-thiazolyl) methyl)amino)carbonyl)-L-valine Methyl Ester

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-isopropyl-4-(((N-(1-propyl))amino)methyl)thiazole provided, after silica gel chromatography using 1% methanol in chloroform as an eluent, 1.55 g (63%) of the desired compound. ^1H NMR ($CDCl_3$) δ 0.86 (t, J=7 Hz, 3H), 1.38 (d, J=7 Hz, 6H), 1.41 (d, J=7 Hz, 6H), 1.56 (m, 1H), 1.57 (sextet, J=7 Hz, 2H), 3.27 (heptet, J=7 Hz, 1H), 3.29 (t, J=7 Hz, 2H), 3.71 (s, 3H), 4.45 (m, 3H), 6.31 (br, 1H), 6.98 (s, 1H). Mass spectrum: $(M+H)^+$=328.

C. N-((N-(1-Propyl)-N-((2-isopropyl-4-thiazolyl) methyl)amino)carbonyl)-L-valine

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 54B provided the desired compound.

D. (2S,3S,5S)-5-(N-(N-((N-(1-Propyl)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl) valinyl)amino)-2-(N-5-thiazolyl)methoxycarbonyl) amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino) carbonyl)-L-valine with N-((N-(1-propyl)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine provided, after silica gel chromatography using 1% methanol in chloroform, 60 mg (44%) of the desired compound (R_f 0.3, 95:5 $CHCl_3$:CH_3OH) as a solid, mp 62°–64° C. Mass spectrum: $(M+H)^+$=721. Anal. Calcd for $C_{37}H_{48}N_6O_5S_2.0.5H_2O$: C, 60.88; H, 6.77: N, 11.51. Found: C, 60.66; H, 6.95; N, 11.45

EXAMPLE 55

A. 2-Isopropyl-4-((N-(isobutyl)amino)methyl) thiazole

Using the procedure of Example 1O, but replacing 40% aqueous methylamine with isobutylamine provided the crude desired compound. Mass spectrum: $(M+H)^+$=213.

B. N-((N-(isobutyl)-N-((2-isopropyl-4-thiazolyl) methyl)amino)carbonyl)-L-valine Methyl Ester

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-isopropyl-4-(((N-(isobutyl))amino)methyl)thiazole provided, after silica gel chromatography using 1% methanol in chloroform as an eluent, 0.7 g (41%) of the desired compound. ^1H NMR (DMSO-d_6) δ 0.78 (d, J=7 Hz, 3H), 0.79 (d, J=7 Hz, 3H), 1.30 (m, 12H), 1.89 (m, 2H), 3.05 (d, J=8 Hz, 2H), 3.22 (m, 1H), 3.58 (s, 3H), 4.13 (m, 1H), 4.44 (AA', 2H), 6.87 (br d, 1H), 7.23 (s, 1H). Mass spectrum: $(M+H)^+$=3.42.

carbonyl)-L-valine with N-((N-methyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine provided, after purification by silica gel chromatography using 1% methanol in chloroform, 50 mg (36%) of the desired compound (R_f 0.40, 5% methanol in chloroform) as a solid, mp 70°–71° C. Mass spectrum: $(M+H)^+$=747. Anal. Calcd for $C_{39}H_{50}N_6O_5S_2$: C, 62.71; H, 6.75; N, 11.25. Found: C, 63.16; H, 6.80; N, 10.84.

EXAMPLE 59

A. 3-Methylbutanamide

Using the procedure of Example 44A but replacing 2-ethylbutyric acid with 3-methylbutyric acid provided 4.2 g (100%) of the crude desired compound.

B. 3-Methylpropanethiocarboxamide

Using the procedure of Example 10, but replacing isobutyramide with 3-methylbutanamide provided the crude desired compound.

C. 4-(Chloromethyl)-2-isobutylthiazole hydrochloride

Using the procedure of Example 1P, but replacing 2-methylpropane thioamide with 3-methylpropanethiocarboxamide provided the crude desired compound as a yellow oil.

D. 2-Isobutyl-4-(((N-methyl)amino)methyl)thiazole

Using the procedure of Example 1Q, but replacing 4-(chloromethyl)-2-isopropylthiazole hydrochloride with 4-(chloromethyl)-2-isobutylthiazole hydrochloride provided, after purification of the residue by silica gel chromatography using 10% methanol in chloroform, 0.61 g (31%) of the desired compound.

E. N-((N-Methyl-N-((2-isobutyl-4-thiazolyl)methyl) amino)carbonyl)-L-valine Methyl Ester

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-isobutyl-4-(((N-methyl)amino)methyl) thiazole provided, after purification by silica gel chromatography using 1% methanon in chloroform as an eluent, 0.40 g (32%) of the desired compound. Mass spectrum: $(M+H)^+$=342.

F. N-((N-Methyl-N-((2-isobutyl-4-thiazolyl)methyl) amino)carbonyl)-L-valine

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 59E provided 0.13 g (70%) of the desired compound.

G. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isobutyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino) carbonyl)-L-valine with N-((N-methyl-N-((2-isobutyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine provided, after purification by silica gel chromatography using 1% methanol in chloroform, 50 mg (33%) of the desired compound (R_f 0.65, 10% methanol in chloroform). Mass spectrum: $(M+H)^+$=735.

EXAMPLE 60

A. 2-Cyclopentyl-4-(((N-ethyl)amino)methyl) thiazole

Using the procedure of Example 1Q, but replacing 4-(chloromethyl)-2-isopropylthiazole hydrochloride with 4-(chloromethyl)-2-cyclopentylthiazole hydrochloride and replacing 40% aqueous methylamine with 70% aqueous ethylamine provided, after purification of the residue by silica gel chromatography using 5% methanol in chloroform, 1.08 g (50%) of the desired compound.

B. N-((N-Ethyl-N-((2-cyclopentyl-4-thiazolyl) methyl)amino)carbonyl)-L-valine Methyl Ester

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-cyclopentyl-4-(((N-ethyl)amino)methyl)-thiazole provided, after purification by silica gel chromatography using 1% methanol in chloroform as an eluent, 0.40 g (46%) of the desired compound. ^{11}H NMR (DMSO-d_6) δ 1.00 (t, J=7Hz, 3H), 1.29 (d, J=7 Hz, 3H), 1.6–1.8 (m, 9H), 2.1 (m, 3H), 3.27 (m, 2H), 3.37 (m, 1H), 3.60 (s, 3H), 4.17 (pentet, J=7 Hz, 1H), 4.41 (AA', 2H), 6.80 (d, J=7 Hz, 1H), 7.20 (s, 1H). Mass spectrum: $(M+H)^+$=340.

C. N-((N-Ethyl-N-((2-cyclopentyl-4-thiazolyl) methyl)amino)carbonyl)-L-valine

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 60B provided 0.13 g (69%) of the desired compound.

D. (2S,3S,5S)-5-(N-(N-((N-Ethyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl) valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl) amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino) carbonyl)-L-valine with N-((N-ethyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine provided, after purification by silica gel chromatography using 1.5% methanol in chloroform, 50 mg (34%) of the desired compound (R_f 0.63, 10% methanol in chloroform) as a solid, mp 67°–69° C. Mass spectrum: $(M+H)^+$=733. Anal. Calcd for $C_{38}H_{48}N_6O_5S_2$: C, 62.27; H, 6.60; N, 11.47. Found: C, 62.02; H, 6.74; N, 10.98.

EXAMPLE 61

A. 2-Isopropyl-4-(2-((N-methyl)amino)ethyl) thiazole

A solution of 2.0 g (12 mmol) of 2-isopropyl-4-(hydroxyethyl)thiazole in 50 ml of tetrahydrofuran was treated with 1.34 g (12 mmol) of methanesulfonyl chloride. The resulting solution was treated dropwise with 3.4 ml (24 mmol) of triethylamine and stirred at ambient temperature for 1 h. A portion (25 ml) of the resulting solution was added to 50 ml of aqueous ethylamine (70% in H_2O) with rapid stirring. After addition, the mixture was heated to reflux for 2 h, allowed to cool, diluted with ethyl acetate, washed with aqueous $NaHCO_3$ and saturated brine, dried over Na_2SO_4, and concentrated in vacuo to provide the crude desired compound. Purification of the residue by silica gel chromatography using 5% methanol in chloroform, 0.52 g (48%) of the desired compound. ^1H NMR ($CDCl_3$) δ 1.38 (d, J=7 Hz,

EXAMPLE 65

A. (2S,3S,5S)-3-(tert-Butyldimethylsilyloxy)-2-(tert-butyloxycarbonylamino)-1-phenyl-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-6-(5-thiazolyl) hexane

Using the procedure of Example 8F, but replacing benzyl alcohol with 5-(hydroxymethyl)thiazole provided, after silica gel chromatography using 10% methanol in dichloromethane, 261 mg (67%) of the desired compound. ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 6H), 0.91 (s, 9H), 1.34 (s, 9H), 1.70 (m, 2H), 2.72 (m, 2H), 3.03 (m, 2H), 3.74 (m, 1H), 3.91 (m, 1H), 4.02 (m, 1H), 4.63 (br d, 1H), 5.24 (s, 2H), 7.19–7.35 (m, 5H), 7.52 (s, 1H), 7.86 (s, 1H), 8.66 (s,1H), 8.79 (s, 1H). Mass spectrum: $(M+H)^+$=647.

B. (2S,3S,5S)-2-(tert-Butyloxycarbonylamino)-1-phenyl-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-6-(5-thiazolyl)-3-hydroxyhexane

Using the procedure of Example 8G, but replacing the resultant compound of Example 8F with the resultant compound of Example 65A provided, after silica gel chromatography using 10% methanol in dichloromethane, 74 mg (35%) of the desired compound. ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9H), 1.65 (m, 2H), 2.87 (m, 2H), 3.09 (m, 2H), 3.68 (m, 2H), 3.96 (m, 2H), 4.74 (br d, 1H), 5.26 (dd, 2H), 7.17–7.32 (m, 5H), 7.52 (s, 1H), 7.86 (s, 1H), 8.66 (s, 1H), 8.81 (s, 1H). Mass spectrum: $(M+H)^+$=533

C. (2S,3S,5S)-2-Amino-1-phenyl-5-(N-((5-thiazolyl) methoxycarbonyl)amino)-6-(5-thiazolyl)-3-hydroxyhexane

A solution of 70 mg (0.13 mmol) of the resultant compound of Example 65B in 2.1 ml of CH_2Cl_2 was treated with 0.7 ml of trifluoroacetic acid, stirred for 1.5 h, and concentrated in vacuo. The residue was treated with 3 ml of aqueous $NaHCO_3$, extracted with three portions of 95:5 CH_2Cl_2:$CHCl_3$, dried over Na_2SO_4, and concentrated in vacuo to provide 55 mg (97%) of the desired compound as a white foamy solid. ^{1}H NMR ($CDCl_3$) δ 1.72 (m, 2H), 1.86 (br, 2H), 2.46 (dd, 1H), 2.84 (m, 2H), 3.20 (m, 2H), 3.45 (m, 1H), 4.02 (m, 1H), 5.30 (dd, 2H), 5.52 (br d, 1H), 7.14–7.34 (m, 5H), 7.59 (s, 1H), 7.88 (s, 1H), 8.67 (s, 1H), 8.80 (s, 1H). Mass spectrum: $(M+H)^+$=433.

D. (2S,3S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl) methoxycarbonyl)valinyl)amino(-1-phenyl-5-(N-((5-thiazolyl)methoxycarbonyl)amino-6-(5-thiazolyl)-3-hydroxyhexane

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino) carbonyl)-L-valine with N-((2-isopropyl-4-thiazolyl) methoxycarbonyl)valine and replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-2-amino-1-phenyl-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-6-(5-thiazolyl)-3-hydroxyhexane provided, after silica gel chromatography using 1% methanol in chloroform, 54 mg (66%) of the desired compound (R_f 0.6, 10% methanol in CH_2Cl_2). ^{1}H NMR (DMSO-d_6) δ 0.69 (d, 3H), 0.74 (d, 3H), 1.31 (d, 6H), 1.47 (m, 2H), 1.85 (m, 1H), 2.75 (m, 4H), 2.95 (m, 1H), 3.57 (m, 1H), 3.80 (m, 2H), 4.08 (m, 1H), 4.95 (d, 1H), 5.03 (s, 2H), 5.19 (s, 2H), 7.12–7.29 (m), 7.45 (s, 1H), 7.47 (s, 1H). Mass spectrum: $(M+H)^+$=715.

EXAMPLE 66

(2S,3S,5S)-2,5-Diamino-3-hydroxy-1,6-diphenylhexane dihydrochloride

EXAMPLE 66A

(L)-N,N-Dibenzylphenylalanine benzyl ester

A solution containing L-phenylalanine (11 kg, 66.7 moles), potassium carbonate (29 kg, 210 moles), and water (66 L), and benzyl chloride (27kg, 213 moles) was heated to 90°±15° C. for 10–24 hours. The reaction mixture was cooled to room temperature and heptane (29 L) and tap water (27 L) was added. The layers were separated and the organics washed one to two times with 22 L of a methanol/water solution (½ v/v). The organics were then stripped to give the desired product as an oil. IR (neat) 3090, 3050, 3030,1730, 1495, 1450, 1160 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5–7.0 (m, 20H), 5.3 (d, 1H, J=13.5 Hz), 5.2 (d, 1H, J=13.5 Hz), 4.0 (d, 2H, J=15 Hz), 3.8 (t, 2H, J=8.4 Hz), 3.6 (d, 2H, J=15 Hz), 3.2 (dd, 1H, J=8.4, 14.4 Hz), ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.0, 139.2, 138.0, 135.9, 129.4, 128.6, 128.5, 128.4, 128.2,128.1, 128.1, 126.9, 126.2, 66.0, 62.3, 54.3, 35.6. $[\alpha]_D$ –79° (c=0.9, DMF).

EXAMPLE 66B

(4S)-4-(N,N-Dibenzylamino)-3-oxo-5-phenyl-pentanonitrile

A solution containing the product of Example 66A (i.e., benzyl ester) (approx. 0.45 moles) in 520 mL tetrahydrofuran and 420 mL acetonitrile was cooled to –40° C. under nitrogen. A second solution containing sodium amide (48.7g, 1.25 moles) in 850 mL tetrahydrofuran was cooled to –40° C. To the sodium amide solution was slowly added 75 mL acetonitrile and the resulting solution was stirred at –40° C. for more than 15 minutes. The sodium amide/acetonitrile solution was then slowly added to the benzyl ester solution at –40° C. The combined solution was stirred at –40° C. for one hour and then quenched with 1150 mL of a 25% (w/v) citric acid solution. The resulting slurry was warmed to ambient temperature and the organics separated. The organics were then washed with 350 mL of a 25% (w/v) sodium chloride solution, then diluted with 900 mL heptane. The organics were then washed three times with 900 mL of a 5% (w/v) sodium chloride solution, two times with 900 mL of a 10% methanolic water solution, one time with 900 mL of a 15% methanolic water solution, and then one time with 900 mL of a 20% methanolic water solution. The organic solvent was removed in vacuo and the resulting material dissolved into 700 mL of hot ethanol. Upon cooling to room temperature, the desired product precipitated. Filtration gave the desired product in 59% yield from the L-phenylalanine. IR ($CHCl_3$) 3090, 3050, 3030, 2250, 1735, 1600, 1490, 1450, 1370, 1300, 1215 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 15H), 3.9 (d, 1H, J=19.5 Hz), 3.8 (d, 2H, J=13.5 Hz), 3.6 (d, 2H, J=13.5 Hz), 3.5 (dd, 1H, J=4.0, 10.5 Hz), 3.2 (dd, 1H, J=10.5, 13.5 Hz), 3.0 (dd, 1H, J=4.0, 13.5 Hz), 3.0 (d, 1H, J=19.5 Hz), ^{13}C NMR (300 MHz, $CDCl_3$) δ 197.0, 138.4, 138.0, 129.5, 129.0, 128.8, 128.6, 127.8, 126.4, 68.6, 54.8, 30.0, 28.4. $[\alpha]_D$ –95° (c=0.5, DMF).

EXAMPLE 66C

Alternate preparation of (4S)-4-(N,N-Dibenzylamino)-3-oxo-5-phenyl-pentanonitrile

To a flask was charged sodium amide (5.8g, 134mmol) under nitrogen followed by 100 mL of methyl t-butyl ether (MTBE). The stirred solution was cooled to 0° C. Acetonitrile (8.6 mL, 165 mmol) was added over 1 minute. This solution was stirred at 5±5° C. for 30 minutes. A solution of (L)-N,N-dibenzylphenylalanine benzyl ester (25 g, 90% pure, 51.6 mmol) in 125 mL of MTBE was added over 15 minutes and the resulting heterogeneous mixture was stirred at 5°±5° C. until the reaction was complete (approx. 3 hours). The reaction was quenched with 100 mL of 25% w/v aqueous citric acid and warmed to 25° C. before separating

(2x200 mL), water (1x200 mL), saturated $NaHCO_3$ (2x200 mL) and water (1x200 mL). The organic solution was then dried over sodium sulfate and concentrated under reduced pressure to provide the desired product as a light yellow oil. 300 MHz ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H), 1.58 (s, 2H), 2.45–2.85 (m, 4H), 3.05 (m, 1H), 3.38 (d, 2H), 3.6 (m, 1H), 3.79 (m, 1H), 3.87 (d, 2H), 4.35 (s, 1H), 4.85 (s, broad, 1H), 7.0–7.38 (m, 20H).

EXAMPLE 67B

(2S,3S,5S)-2-amino-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane

To a stirred solution of (2S,3S,5S)-2-(N,N-dibenzylamino)-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane (12 g, 21.3 mmol) in methanol (350 mL) was charged ammonium formate (8.05 g, 128 mmol, 6.0 eq) and
10% palladium on carbon (2.4 g). The solution was stirred under nitrogen at 60° C. for three hours and then at 75° C. for 12 hours. An additional amount of ammonium formate (6 g) and 10% palladium on carbon (1.5 g) was added as well as 1 mL of glacial acetic acid. The reaction was driven to completion within 2 hours at a reflux temperature. The reaction mixture was then cooled to room temperature and then filtered through a bed of celite. The filter cake was washed with methanol (75 mL) and the combined filtrates were concentrated under reduced pressure. The residue was taken up in 1N NaOH (300 mL) and extracted into methylene chloride (2x200 mL). The combined organic layers were washed with brine (250 mL) and dried over sodium sulfate. Concentration of the solution under reduced pressure provided the desired product as a light colored oil which slowly crystallized upon standing (5 g). Further purification of the product could be accomplished by flash chromatography (silica gel, 5% methanol in methylene chloride). 300 MHz ^1H NMR ($CDCl_3$) δ 1.42 (s, 9H), 1.58 (m, 1H), 1.70 (m, 1H), 2.20 (s, broad, 2H), 2.52 (m, 1H), 2.76–2.95 (m, 4H), 3.50 (m, 1H), 3.95 (m, 1H), 4.80 (d, broad, 1H), 7.15–7.30 (m, 10H).

EXAMPLE 68

Alternative Preparation of (2S,3S,5S)-2-Amino-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane

EXAMPLE 68A

(5S)-2-(t-Butyloxycarbonylamino)-5-(N,N-dibenzylamino)-1,6-diphenyl-4-oxo-2-hexene

To 9.21 gm (20 mmol) of the resultant compound of Example 66D and 0.37 gm (3 mmol) 4-N,N-dimethylaminopyridine in 100 ml of methyl tert-butylether was added via syringe pump a solution containing 4.80 gm (22 mmol) di-tert-butyl dicarbonate in the same solvent (25 ml) over a period of 6 h. An additional amount (3 ml) of methyl tert-butylether was then added to complete the addition. After stirring at room temperature for 18 h the reaction mixture was cooled with the aid of an ice water bath. The resultant solid was collected by suction filtration and washed with cold (0° C.) methyl tert-butylether and hexane and dried under vacuum to give 9.9 gm of crude material as a white solid. The material thus isolated was dissolved in a minimal amount of dichloromethane and purified by flash chromatography on silica gel. Elution of the column with a mixture of hexane-ethyl acetate dichloromethane (8:1:1) gave, after concentration of the appropriate fractions, 8.1 gm (72%) of the desired compound. Mp. 191°–193° C. $[\alpha]_D$ −183.7° (c=1.05, $CHCl_3$). ^1H NMR ($CDCl_3$, δ): 11.68 (bs, 1H), 7.05–7.47 (m, 20H), 5.28 (s, 1H), 4.27 (d, J=16 Hz, 1H), 4.02 (d, J=16Hz, 1H), 3.58 (m, 4H), 3.40 (m, 1H), 3.11 (m, 1H), 2.90 (m, 1H), 1.48 (s, 9H).

EXAMPLE 68B

Alternate preparation of (5S)-2-(t-Butyloxycarbonylamino)-5-(N,N-dibenzylamino)-1,6-diphenyl-4-oxo-2-hexene

A suspension of (S)-2-amino-5-(N,N-dibenzylamino)-1,6-diphenyl-4-oxo-2-hexene (100.0 g, 0.217 mol) in 15% ethyl acetate/hexanes (2 liters) under N_2 was warmed to about 40° C. The resulting solution was cooled to room temperature before adding 4.0 g (33 mmol) of N,N-dimethyl-4-aminopyridine and 49.7 g (0.228 mol) of di-tert-butyl dicarbonate. The reaction mixture was allowed to stir overnight at room temperature. (After approximately one hour, a white precipitate began to form.) The suspension was filtered and the precipitate was washed with hexanes to afford the desired product as colorless crystals. TLC: 25% ethyl acetate/hexanes R_f 0.38.

EXAMPLE 68C

(2S,3S,5S)-2-(N,N-Dibenzylamino)-5-(t-butyloxycarbonylamino)-3-hydroxy-1,6-diphenylhexane

A solution of the product of Example 68A (5 g, 8.9mmol) in dichloromethane (100ml) and 1,4-dioxolane (100ml) was cooled to between −10° and −15° C. and treated dropwise with 1M BH_3THF (26.7ml, 26.7mmol). The solution was stirred at this temperature for 3 hr. The clear solution was quenched with excess methanol (20ml) and stirred at room temperature for 30 min. The solvent was removed in vacuo.

The resulting white foam was dissolved in THF (75ml) and cooled to −40° C. A solution of LAH (9ml, 1M in THF, 9mmol) was added dropwise. After 10 min. the solution was quenched with water followed by dilute aqueous HCl. The organics were removed and the aqueous layer extracted with ethyl acetate (3x20 ml). The combined organics were washed (saturated aqueous bicarbonate followed by brine), dried (Na_2SO_4), filtered and evaporated to afford 4.9 g (99%) of the desired product as a white foam.

Alternatively, the white foam resulting from the BH_3THF reaction step was dissolved in MeOH (45ml), cooled to +3° C. and treated portionwise with KBH_4 (1.44 g, 26.7 mmol). After addition of the last portion of KBH_4 the reaction was stirred for an additional 4 hours at +4° to +5° C. The solution was concentrated by ½ the volume in vacuo, diluted with 1/1 hexane-EtOAc (70 ml) and quenched (with cooling, maintain temp. <30°C.) by adding a 10% solution of $KHSO_4$ to pH=about 5. NaOH (15% aqueous) was added to pH=12–13. The insoluble salts were removed by filtration, and the filter cake washed 3 times with 7 ml 1/1 hexane/EtOAc. The filtrate and washes were transferred to a separatory funnel, diluted with 15 ml hexane and 15 ml H_2O. The organics were removed and the aqueous layer was extracted once with 20 ml (1/1) hexane-EtOAc. The combined organics were washed (saturated brine), dried (Na_2SO_4), filtered, and evaporated to afford 5.2 g of the desired product which was used without further purification in subsequent reactions.
R_f 0.5 (25% EtOAc/hexane) ^1H NMR ($CDCl_3$) δ 7.37–7.10 (m 20H); 6.78 (br. s, 1H); 4.62 (d, 1H); 4.50 (s, 1H); 4.18

-60° C. A solution of 5-(p-nitrophenyloxycarbonyloxymethyl)thiazole (9.5 g, 33.5 mmol) in DMF (50 mL) was added over 45 minutes. The resulting mixture was stirred for 8 hours at -55°±5° C., then 14 hours at -25° C., then was allowed to warm to room temperature. The reaction mixture was diluted with 1N HCl (250 mL) and washed with CH_2Cl_2 (2×80 mL). The combined organic layers were back-extracted with 1N HCl (60 mL). The combined aqueous HCl layers were cooled in an ice-bath to 2° C., and conc. (37%) HCL (30 mL) was added over 5 minutes. The desired product (bis HCl salt) began to precipitate within 30 minutes. The slurry was stirred 3 hours at 2°-5° C., then the product (bis HCl salt) was collected by filtration and dried in a vacuum oven at 55°-60° C. Yield 11.4 g (68%).

Second crop recovery:

The HCl mother liquors were stirred with ethyl acetate (190 mL) and neutralized to pH 9-10 with aqueous K_2CO_3 (200-300 g of 25% w/w K_2CO_3 was required). The ethyl acetate layer was concentrated under vacuum to an oil which was redissolved in 1N HCl (90 mL) and washed with methylene chloride (45 mL). The aqueous layer was cooled to 2° C. Conc. (37%) HCl (9.0 mL) was added to precipitate a second crop. After stirring for 1-3 hours at 2-5° C., the solid was collected by filtration and dried in a vacuum oven at 55°-60° C. Yield 2.1 g (12.6%).

Neutralization of Bis HCl Salt:

The bis HCl salt (10.66 g, 21.4 mmol, mixture of first and second crops) was stirred with CH_2Cl_2 (110 mL) and 5% aqueous $NaHCO_3$ (110 mL) until all solids dissolved (2 hours). The aqueous layer was separated and extracted with another 50 mL CH_2Cl_2. The combined organic extracts were dried with Na_2SO_4 (10 g), filtered and concentrated under vacuum at ≦40° C. to an oil. The oil was dried on a vacuum pump to give the title compound as a yellow foam, 9.1 g (100%).

Alternative B

The product of Example 66F (15.0 g, 0.053 mole) was dissolved in DMF (75 mL). Triisopropylborate (24.4 mL, 0.105 mole) was added and stirred at ambient temperature for approximately 1.5 hours. The solution was cooled to -10° C. and a solution of 5-(p-nitrophenyloxycarbonyloxymethyl)thiazole (15.0 g, 0.054 mole) in DMF (75 mL) was added over 80 minutes. The reaction was stirred for approximately 1 hour at -10° C., then was diluted with methylene chloride (250 mL) and quenched with a mixture of triethanolamine (24.8 g) and 5% aqueous sodium bicarbonate (300 mL). The biphasic mixture was stirred for 1 hour, then the layers were separated and the aqueous was extracted with another portion of methylene chloride (50 mL). The combined organic layers were extracted with 1N HCl (1×390 mL, then 1×95 mL). The acid layers were combined, cooled in an ice-bath, and further acidified with conc. HCl (50 mL) which produced a white slurry of product. The slurry was stirred for approximately 1 hour at 2° C. The desired product bis HCl salt) was collected by filtration and dried at 55° C. in a vacuum oven. Yield 18.5 g (70%).

EXAMPLE 71

Alternative Preparation of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino) carbonyl)valinyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

To a solution of the product of Example 70 (9.1 g, 21.4 mmol), HOBT (3.6 g, 23.5 mmol) and N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)-carbonyl)-L-valine (7.37 g, 23.5 mmol) in THF (170 mL) was added DCC (4.85 g, 23.5 mmol). The solution was stirred at ambient temperature for 16 hours (DCU precipitates). THF was removed under vacuum and the resulting paste was stirred with cold 1N HCl (106 mL at 5° C.) for 3 hours to dissolve the the crude product. The DCU was removed by filtration and the filter cake was washed with 1N HCl (30 mL). KH_2PO_4 (3.2 g) was dissolved in the combined HCl filtrates. The solution was mixed with ethyl acetate (80 mL) and neutralized to pH 7 with aqueous NaOH (60.3 g of 10% w/w NaOH). The aqueous layer was extracted with another 25 mL ethyl acetate and the combined ethyl acetate extracts were washed with aqueous $NaHCO_3$ (2×37 mL of 5% w/w $NaHCO_3$). The organic layer was dried with Na_2SO_4 (13 g), filtered, and concentrated under vacuum at ≦45° C. The residue was dissolved in a 1:1 ethyl acetate/heptane mixture (200 mL) at 70° C. The solution was allowed to cool slowly and stirred overnight at room temperature to provide a thick slurry. The product was collected by filtration and washed with 1:1 ethyl acetate/heptane (20 mL). The product was dried briefly at 55° C. in a vacuum oven to obtain an approximate weight prior to the second crystallization (12.85 g, 83%).

A second crystallization from 144 mL of 2:1 ethyl acetate/heptane (dissolved at ~70° C., then stirred at room temperature 12 hours) produced a thick slurry of fine white solid. The product was collected by filtration and washed with 15 mL 2:1 ethyl acetate/heptane, then dried in a vacuum oven at 55° C. for 2 days to give the desired product. Yield 11.9 g (77%).

EXAMPLE 72

Alternate Preparation of ((5-Thiazolyl)methyl)-(4-nitrophenyl)carbonate

EXAMPLE 72A

2-Amino-5-(ethoxycarbonyl)thiazole Hydrochloride

To a -10° C. solution of potassium tert-butoxide (110 g, 0.98 mol) in THF (1.9 L) was added a solution of ethyl chloroacetate (100 mL, 0.934 mol) and ethyl formate (75 mL, 0.928 mol) in THF (400 mL) dropwise over 2 hours, with good mechanical stirring. The thick solution was stirred another 2 hours at ca. -1° C. then the reaction was quenched by addition of a solution of NaCl (150 g) in 1N HCL (750 mL). The mixture was allowed to warm to 20° C. and the lower aqueous layer (containing some precipitated salt) was separated. The organic layer was stripped under vacuum on a rotary evaporator. The oil was redissolved in 500 mL ethyl acetate, dried with 75 g Na_2SO_4 for 1 hour, filtered and concentrated under vacuum (40°-50° C. bath temperature) to an oil. The resulting crude chloroaldehyde (161 g) and thiourea (70 g, 0.92 mol) were dissolved in THF (2 L) and warmed to gentle reflux (60° C.). The thiourea dissolved during warming, and within 20 minutes, product precipitated from solution. After 100 minutes the suspension was allowed to cool to room temperature, then was cooled in an ice-bath for 1 hour. The product was collected on a fritted Buchner funnel and washed with 2×100 mL cold THF, then dried overnight in a vacuum oven at 50° C. Yield: 122 g of title compound as a tan-colored solid, m.p. 182°-185° C. (dec.). ^1H NMR (DMSO-d_6) δ 7.86 (s, 1H), 4.19 (q, 2H), 1.21 (t, 3H). ^{13}C NMR (DMSO-d_6) δ 171.9, 160.4, 140.4, 114.4, 61.1, 14.2.

EXAMPLE 72B

2-Amino-5-(ethoxycarbonyl)thiazole

To a -10° C. solution of potassium tert-butoxide (150 g, 1.3 mol) in THF (1.35 L) was added a solution of ethyl

ics reduced under vacuum to an oil. The oil was dissolved in 50 mls THF and again the solvent was removed under vacuum to give the desired product as a yellow oil. (yield approx. 27 grams, 88%).

EXAMPLE 73B

2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole

The thioisobutyramide resulting from Example 73A was dissolved in 70 mls THF and added slowly to a solution of (34.1 g , 0.27 mols) 1,3-dichloracetone in 40 mls THF. A 10 ml rinse of THF was used to completely transfer the thioamide. The reaction was carried out in a 250 ml flask with mechanical stirring under nitrogen atmosphere. The reaction temperature was maintained below 25° C. during addition with a 15°±5° C. bath. The bath was kept in place for 1 hour after which it was removed and the reaction stirred for 18 hours. Next this stirred chloromethyl-thiazole solution was added to 376 mls (4.37 mols) 40% aqueous methylamine solution at 15° C. in a 1 liter flask. The temperature was maintained below 25° C. during addition. After half an hour the bath was removed and the reaction stirred for 3 hours at ambient temperature. The solvent was removed under vacuum with a 50° C. bath to an end volume of 310 mls. The residue was then basified with 50 g 10% NaOH to pH 12 and extracted into methylene chloride (2×160 mls). The combined organics were then washed with 1×150 g of 20% ammonium chloride followed by 1×90 g of 20% ammonium chloride. The combined aqueous washes were then back extracted with 150 mls methylene chloride. The combined product methylene chloride layers were then extracted with 100 g of a solution of 25 g conc. HCl and 75 g water. This acidic product solution was then washed with 135 mls methylene chloride. Next the acidic product solution was cooled, then neutralized with 100 g 20% NaOH solution. The product was extracted from this mixture with methylene chloride (2×135 mls). The solvent was removed under vacuum to afford the desired product as an amber oil. (yield approx. 28 grams)

EXAMPLE 73C

N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl) amino)carbonyl)-L-valene Methyl Ester

Into a 500 ml 3-neck round bottom flask equipped with mechanical stirrer, nitrogen atmosphere, thermocouple, heating mantle and condensor was charged the product of Example 73B (28.1 g, 0.165 mols), phenoxycarbonyl-(L)-valine (41.5 g, 0.165 mol) and 155 ml toluene. This solution was warmed to reflux (110° C.) and stirred for three hours, then cooled to 20°±5° C. and washed with 2×69 ml 10% citric acid followed by 1'69 ml water, 1×116 mls 4% sodium hydroxide, 1×58 ml 4% sodium hydroxide and finally 1×58 ml water. The organic product solution was then treated with 3 grams of activated carbon at reflux for 15 minutes, filtered through infusorial earth to remove carbon, and the carbon/infusorial earth cake was washed with 25 ml hot toluene. Next the solvent was removed to afford a brown oil which solidifed upon cooling. This brown solid was dissolved with warming in 31 ml EtOAc and 257 ml heptane at 60°±5° C. This solution was slowly cooled to 25° C., stirred 12 hours, cooled further to 0° C., and stirred 3 hours. The crystals were collected by filtration and washed with 50 ml 1:9 EtOAc/Heptane. The solid was dried in a 50° C. vacuum oven for 12 hours to afford 41.5 grams of the desired product as a tan-colored solid (76.9%).

EXAMPLE 73D

N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl) amino)carbonyl)-L-valine

To a one liter three neck flask was charged the product of Example 73C (50 g, 0.153 mol), lithium hydroxide monohydrate (13 g, 0.310 mol), 200 ml THF and 190 ml water. This hazy solution was stirred for 2 hours. The reaction was quenched with a solution of conc. HCl (32.4 g, 0.329 mol) in 65 mL water, the THF was removed under vacuum and the product extracted into methylene chloride (3×210 ml). (NOTE: If necessary, the pH of the aqueous layer should be adjusted to maintain pH 1–4 during the extractions.) The combined organics were then dried with 50 g sodium sulfate, filtered with a 150 ml methylene chloride rinse of the sodium sulfate, and the solvent was removed under vacuum. The product was dissolved in 450 ml THF and again the solvent was removed. Next the product was dissolved in 475 ml THF containing 0.12 g butylated hydroxytoluene (BHT) for storage. If desired, the solvent can be removed under vacuum and the residual syrup dried in a vacuum oven at 55° C. to provide a glassy solid.

Fluorogenic Assay for Screening Inhibitors of HIV Protease

The inhibitory potency of the compounds of the invention can be determined by the following method.

A compound of the invention is dissolved in DMSO and a small aliquot further diluted with DMSO to 100 times the final concentration desired for testing. The reaction is carried out in a 6×50 mm tube in a total volume of 300 microliters. The final concentrations of the components in the reaction buffer are: 125 mM sodium acetate, 1M sodium chloride, 5 mM dithiothreitol, 0.5 mg/ml bovine serum albumin, 1.3 μM fluorogenic substrate, 2% (v/v) dimethylsulfoxide, pH 4.5. After addition of inhibitor, the reaction mixture is placed in the fluorometer cell holder and incubated at 30° C. for several minutes. The reaction is initiated by the addition of a small aliquot of cold HIV protease. The fluorescence intensity (excitation 340 nM, emmision 490 nM) is recorded as a function of time. The reaction rate is determined for the first six to eight minutes. The observed rate is directly proportional to the moles of substrate cleaved per unit time. The percent inhibition is 100×(1–(rate in presence of inhibitor)/(rate in absence of inhibitor)).

Fluorogenic substrate: Dabcyl-Ser-Gln-Asn-Tyr-Pro-Ile-Val-Gln-EDANS wherein DABCYL=4-(4-dimethylaminophenyl)azobenzoic acid and EDANS=5-((2-aminoethyl) amino)-naphthalene-1-sulfonic acid.

Table 1 shows the inhibitory potencies of compounds of the invention against HIV-1 protease.

TABLE 1

Compound of Example	Percent Inhibition	Inhibitor Concentration (nanomolar)
1	79	0.5
3	70	0.5
4	72	0.5
5	79	0.5
6	75	0.5
7	74	0.5
9	64	0.5
10	56	0.5
11	71	0.5
12	72	0.5
13	46	0.5
14	61	0.5
15	57	0.5
17	66	0.5
18	80	0.5
19	70	0.5

dently selected from hydrogen, loweralkyl and haloalkyl, or an amino-acyl residue of the formula $R_{180}NH(CH_2)_2NHCH_2C(O)$— or $R_{180}NH(CH_2)_2OCH_2C(O)$— wherein R_{180} is hydrogen, loweralkyl, arylalkyl, cycloalkylalkyl, alkanoyl, benzoyl or an a-amino acyl group. The amino acid esters of particular interest are glycine and lysine; however, other amino acid residues can also be used, including those wherein the amino acyl group is $—C(O)CH_2NR_{200}R_{201}$ wherein R_{200} and R_{201} are independently selected from hydrogen and loweralkyl or the group $—NR_{200}R_{201}$ forms a nitrogen containing heterocyclic ring. These esters serve as pro-drugs of the compounds of the present invention and serve to increase the solubility of these substances in the gastrointestinal tract. These esters also serve to increase solubility for intravenous administration of the compounds. Other prodrugs include a hydroxyl-substituted compound of formula A or A1 or A2 wherein the hydroxyl group is functionalized with a substituent of the formula $—CH(R_g)OC(O)R_{181}$ or $—CH(R_g)OC(S)R181$ wherein R_{181} is loweralkyl, haloalkyl, alkoxy, thioalkoxy or haloalkoxy and R_g is hydrogen, loweralkyl, haloalkyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl or dialkylaminocarbonyl. Such prodrugs can be prepared according to the procedure of Schreiber (Tetrahedron Lett. 1983, 24, 2363) by ozonolysis of the corresponding methallyl ether in methanol followed by treatment with acetic anhydride.

The prodrugs of this invention are metabolized in vivo to provide the hydroxyl-substituted compound of formula A or A1 or A2. The preparation of the prodrug esters is carried out by reacting a hydroxyl-substituted compound of formula A or A1 or A2 with an activated amino acyl, phosphoryl, hemisuccinyl or acyl derivative as defined above. The resulting product is then deprotected to provide the desired pro-drug ester. Prodrugs of the invention can also be prepared by alkylation of the hydroxyl group with (haloalkyl) esters, transacetalization with bis-(alkanoyl)acetals or condensation of the hydroxyl group with an activated aldehyde followed by acylation of the intermediate hemiacetal.

The compounds of the invention are useful for inhibiting retroviral protease, in particular HIV protease, in vitro or in vivo (especially in mammals and in particular in humans). The compounds of the present invention are also useful for the inhibition of retroviruses in vivo, especially human immunodeficiency virus (HIV). The compounds of the present invention are also useful for the treatment or prophylaxis of diseases caused by retroviruses, especially acquired immune deficiency syndrome or an HIV infection in a human or other mammal.

Total daily dose administered to a human or other mammal host in single or divided doses may be in amounts, for example, from 0.001 to 300 mg/kg body weight daily and more usually 0.1 to 10 mg. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

The compounds of the present invention may be administered orally, parenterally, sublingually, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparations, for example, sterile injectable aqueous or oleagenous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-propanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically aceptable and metabolizable lipid capabale of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natureal and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., *Methods in Cell Biology*, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

One preferred dosage form for the compounds of the invention comprises a solid dosage form for oral administration comprising a pharmaceutically acceptable adsorbent to which is adsorbed a mixture of (1) a pharmaceutically acceptable organic solvent or a mixture of two or more pharmaceutically acceptable organic solvents, (2) a compound of the invention in the amount of from about 10% to

It will be understood that agents which can be combined with the compounds of the present invention for the treatment or prophylaxis of AIDS or an HIV infection are not limited to those listed above, but include in principle any agents useful for the treatment or prophylaxis of AIDS or an HIV infection.

When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

What is claimed is:

1. A combination pharmaceutical agent for the treatment of an HIV infection comprising (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino) carbonyl)valinyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane or a pharmaceutically acceptable salt thereof and another HIV protease inhibiting compound.

2. The combination of claim 1 wherein the other HIV protease inhibiting compound is selected from the group consisting of Ro 31-8959, SC-52151, KNI-227 and KNI-272.

3. The combination of claim 1 wherein the other HIV protease inhibiting compound is Ro 31-8959.

4. The combination of claim 1 wherein (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino) carbonyl)valinyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane or a pharmaceutically acceptable salt thereof and the other HIV protease inhibiting compound are each formulated as separate compositions.

5. The combination of claim 4 wherein the formulation of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl) methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane or a pharmaceutically acceptable salt thereof and the formulation of the other HIV protease inhibiting compound are to be administered at the same time.

6. The combination of claim 4 wherein the formulation of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane or a pharmaceutically acceptable salt thereof and the formulation of the other HIV protease inhibiting compound are to be administered at different times.

7. A combination pharmaceutical agent for the treatment of an HIV infection comprising (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino) carbonyl)valinyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane or a pharmaceutically acceptable salt thereof and Ro 31-8959.

8. A combination of pharmaceutical agents for the treatment of an HIV infection comprising (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino) carbonyl)valinyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)-amino)-1,6-diphenyl- 3-hydroxyhexane or a pharmaceutically acceptable salt thereof and another HIV protease inhibiting compound.

9. The combination of claim 8 wherein the other HIV protease inhibiting compound is selected from the group consisting of Ro 31-8959, SC-52151, KNI-227 and KNI-272.

10. The combination of claim 8 wherein the other HIV protease inhibiting compound is Ro 31-8959.

11. The combination of claim 8 wherein (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane or a pharmaceutically acceptable salt thereof and the other HIV protease inhibiting compound are each formulated as separate compositions.

12. The combination of claim 11 wherein the formulation of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane or a pharmaceutically acceptable salt thereof and the formulation of the other HIV protease inhibiting compound are to be administered at the same time.

13. The combination of claim 11 wherein the formulation of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane or a pharmaceutically acceptable salt thereof and the formulation of the other HIV protease inhibiting compound are to be administered at different times.

14. A combination of pharmaceutical agents for the treatment of an HIV infection comprising (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino) carbonyl)valinyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane or a pharmaceutically acceptable salt thereof and Ro 31-8959.

15. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane or a pharmaceutically acceptable salt thereof and another HIV protease inhibitor for concomitant administration for the treatment of an HIV infection.

16. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane or a pharmaceutically acceptable salt thereof and Ro 31-8959 for concomitant administration for the treatment of an HIV infection.

17. A combination pharmaceutical agent for administration to a human for the treatment of an HIV infection comprising:

a) a first pharmaceutical composition comprising (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl) methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane or a pharmaceutically acceptable salt thereof and

b) a second pharmaceutical composition comprising another HIV protease inhibiting compound.

18. The combination of claim 17 wherein the other HIV protease inhibiting compound is selected from the group consisting of Ro 31-8959, SC-52151, KNI-227 and KNI-272.

19. The combination of claim 17 wherein the other HIV protease inhibiting compound is Ro 31-8959.

* * * * *

9/18/00	Serial No. 375	Initial (00P-062-0097442-01, M99-046)
9/18/00	Serial No. 374	Initial (00P-028-0097232-00, M99-046)
9/18/00	Serial No. 373	1st follow up (00P-144-0096039-00, M99-046)
9/18/00	Serial No. 372	1st follow up (00P-163-0094982-00(1), M99-046)
9/18/00	Serial No. 371	1st follow up (00P-163-0096793, M99-046)
9/14/00	Serial No. 370	**Draft Protocol M98-863 Amend 4**
9/12/00	Serial No. 369	**Informal Pancreatitis Report**
9/12/00	Serial No. 368	1st follow up (00P-163-96710-00, M99-046)
9/12/00	Serial No. 367	2nd follow up (00P-163-0096484-00, M99-046)
9/12/00	Serial No. 366	3rd follow up (00P-062-0089902-00, M99-046)
9/8/00	Serial No. 365	Initial Safety
9/8/00	Serial No. 364	1st follow Up (00P-163-0096863-00, M99-046)
9/8/00	Serial No. 363	1st follow up (00P-062-0090740-00, M99-046)
9/5/00	Serial No. 362	1st follow up (00P-028-0096968-00(1), M99-046)
9/5/00	Serial No. 361	2nd follow up (00P-028-0089681-02, M99-046)
8/31/00	Serial No. 360	Initial (00P-028-0096968-00, M99-046)
8/31/00	Serial No. 359	Initial (00P-163-0096863-00, M99-046)
8/31/00	Serial No. 358	Initial (00P-163-0096967-00, M99-046)
8/30/00	Serial No. 357	Initial (00P-163-0096793-00, M99-046)
8/30/00	Serial No. 356	1st Follow Up (00P-163-0096484-00, M99-046)
8/30/00	Serial No. 355	1st Follow Up (00P-163-0090406-00, M99-046)

8/28/00	Serial No. 354	Amend Protocol (M99-056 (5&6) M99-056 (2))
8/28/00	Serial No. 353	1st Follow up(00P-163-0088826-00, M99-046)
8/28/00	Serial No. 352	3rd Follow Up(00P-163-0087658-00, M99-046)
8/28/00	Serial No. 351	Initial (00P-163-0096710-00, M99-046)
8/28/00	Serial No. 350	Initial (00P-008-0096601, Aust PNB)
8/25/00	Serial No. 349	1st follow up (00P-163-0096056-00)
8/25/00	Serial No. 348	Initial (00P-163-0096656-00)
8/21/00	Serial No. 347	Initial (00P-163-0096484-00)
8/21/00	Serial No. 346	Initial (00P-056-0096541-00)
8/21/00	Serial No. 345	Initial (00P-056-0096538-00)
8/18/00	Serial No. 344	**Informal Pancreatitis Report**
8/15/00	Serial No. 343	Initial (00P-163-0096125-00, M99-046)
8/11/00	Serial No. 342	1st Follow up (00P-163-0089677-00(1), M98-863)
8/11/00	Serial No. 341	Initial (00P-144-0096039-00(0), M99-046)
8/11/00	Serial No. 340	Initial (00P-163-0096056-00(0), M99-046)
8/11/00	Serial No. 339	Initial (00P-163-0096122-02(0), M99-046)
8/11/00	Serial No. 338	1st Follow up (00P-143-0095390-00(1), M99-046)
8/11/00	Serial No. 337	Initial (00P-056-0095950-00(0), PNB)
8/7/00	Serial No. 336	**Pharm/Tox Amend** (2 wk monkey study, R&D/00/275)
8/4/00	Serial No. 335	3rd Follow up (00P-163-0089963-03(3), M99-046)
8/4/00	Serial No. 334	**Protocol Amendment** (M99-046, 5.1)
8/3/00	Serial No. 333	Initial (00P-163-0095869-00, M99-046)
8/3/00	Serial No. 332	2nd Follow Up (00P-163-0095305-00(2), M99-046)

8/3/00	Serial No. 331	1st Follow Up (00P-056-0095472-01(1), PNB)
8/3/00	Serial No. 330	1st Follow Up (00P-163-0095305-00(1), M99-046)
8/3/00	Serial No. 329	5th Follow Up (00P-056-0087030-00, M99-046)
8/3/00	Serial No. 328	1st Follow Up (00P-056-0094787-00, PNB)
7/31/00	Serial No. 327	1st Follow Up (00P-056-0095038-00, PNB)
7/31/00	Serial No. 326	Initial (00P-083-0095491-00, M99-046)
7/31/00	Serial No. 325	3rd Follow Up ((54008M) 00P-163-0004835-00, M98-863)
7/31/00	Serial No. 324	1st Follow up (00P-163-0090878, M99-046)
7/25/00	Serial No. 323	1st Follow up (00P-163-0091138-00, M99-046)
7/24/00	Serial No. 322	1st Follow up (00P-163-0090155, M99-046)
7/24/00	Serial No. 321	Initial (00P-056-0095472-01, PNB)
7/24/00	Serial No. 320	1st follow up (00P-163-0095060-01, M99-046)
7/24/00	Serial No. 319	2nd follow up (00P-163-0091253-02, M99-046)
7/24/00	Serial No. 318	Initial (00P-163-0095305-00, M99-046)
7/24/00	Serial No. 317	Initial (00P-143-0095390-00, M99-046)
7/20/00	Serial No. 316	Initial (00P-056-0095038-00(0), PNB)
7/20/00	Serial No. 315	2nd Follow up IND Safety (00P-056-0089245-00, M99-046)
7/19/00	Serial No. 314	**New Protocol** (M99-049, Amend 2, Original submission)
7/18/00	Serial No. 313	**Pancreatitis Informal Report**
7/14/00	Serial No. 312	Initial (00P-163-0095060-01(0), M99-046)
7/14/00	Serial No. 311	Initial (00P-008-0094887-00, AUST-00-001-SAS)
7/14/00	Serial No. 310	Initial (00P-163-0094982-00, M99-046, 7-day 7/10/00)

7/14/00	Serial No. 309	**Protocol Amendment** (M99-046, #4.1)
7/13/00	Serial No. 308	**X-Ref letter** (ACTG A5015)
7/13/00	Serial No. 307	**New Protocol** (M00-154)
7/11/00	Serial No. 306	2nd Follow Up (00P-163-0091292, M99-046)
7/11/00	Serial No. 305	Initial (00P-163-0094833-00, M99-046, 7-day 6/30)
7/11/00	Serial No. 304	Initial (00P-05600094788, PNB, 7-day 6/30, no longer expedited)
7/11/00	Serial No 303	Initial (00P-056-0094787-00, PNB, 7-day 6/30))
7/10/00	Serial No. 302	1st Follow up (00P-163-0091253-01, M99-046)
7/10/00	Serial No. 301	1st Follow Up (00P-163-0091292, M99-046)
7/10/00	Serial No. 300	1st Follow up (00P-163-0090733, M99-046)
7/6/00	Serial No. 299	New Investigator
7/5/00	Serial No. 298	Initial (00P-163-0091138-00, M99-046)
6/30/00	Serial No. 297	Initial (00P-163-0091253, M99-046)
6/30/00	Serial No. 296	Initial (00P-163-0091292, M99-046)
6/29/00	Serial No. 295	Initial (00P-163-0091203, M99-046)
6/27/00	Serial No. 294	1st follow up (00P-163-0090794-00, M99-046)
6/27/00	Serial No. 293	Initial (00P-163-0090878-00, M99-046)
6/23/00	Serial No. 292	Corrected Report (00P-143-0089087, M98-940)
6/23/00	Serial No. 291	1st follow up (00P-163-0090421-00(1), M99-046)
6/19/00	Serial No. 290	2nd Follow Up (00P-163-0090388, M99-046)
6/19/00	Serial No. 289	Initial (00P-062-0090740-00(0), M99-046)
6/19/00	Serial No. 288	Initial (00P-163-0090406-00, M99-046, 7 day 6/13)

6/16/00	Serial No. 287	Initial (00p-163-0090794, M99-046, 7 day 6/14)
6/16/00	Serial No. 286	Initial (00P-163-0090733, M99-046, 7 day 6/13)
6/16/00	Serial No. 285	2nd follow up (00P-062-0089902-00(2), M99-046)
6/14/00	Serial No. 284	3rd FollowUp (00P-056-0086577-00(3), M98-957)
6/13/00	Serial No. 283	X-ref Letter to Gilead for GS-00-909
6/9/00	Serial No. 282	2nd Follow up (00P-163-0089963-03(2), M99-046)
6/9/00	Serial No. 281	Initial (00P-163-0090491-00, M99-046)
6/9/00	Serial No. 280	Initial (00P-163-0090496-00, M99-046)
6/9/00	Serial No. 279	Initial Written (00P-163-0090515-00(0), M99-046)
6/9/00	Serial No. 278	1st Follow up (00P-163-0090388-009(1), M99-046)
6/8/00	Serial No. 277	Initial (00P-056-009045700(0), PNB)
6/8/00	Serial No. 276	Initial (00P-163-0090421-00(0), M99-046)
6/6/00	Serial No. 275	New Investigator
6/6/00	Serial No. 274	1st Follow up (00P-056-0089847-00(1), M99-046)
6/6/00	Serial No. 273	Initial written (00P-163-0090388-00, M99-046)
6/5/00	Serial No. 272	3rd Follow up (00P-163-0089392-00(3), M99-046)
6/5/00	Serial No. 271	1st Follow up (00P-056-0089245-00(1), M99-046)
6/2/00	Serial No. 270	1st follow up (00P-028-0089681-02(1), M99-046)
6/2/00	Serial No. 269	**Change in Protocol** (M99-046 #2 and M98-863 #3)
6/2/00	Serial No. 268	Initial (00P-163-0090352, M99-046)
6/2/00	Serial No. 267	2nd follow up (00P056-0089644, M99-046)
6/2/00	Serial No. 266	2nd follow up (00P-056-0086577, M98-957)
6/2/00	Serial No. 265	1st follow up (00P-163-0089904, M99-046)

5/30/00	Serial No. 264	1st Follow up (00P-062-0089902-00(1), M99-046)
5/30/00	Serial No. 263	1st Follow up (00P-163-0089963-03(1), M99-046)
5/30/00	Serial No. 262	1st Follow up (00P-143-0089575-00(1), M98-863)
5/30/00	Serial No. 261	2nd Follow up (00P-163-0089392-00(2), M99-046)
5/30/00	Serial No. 260	Initial Report (00P-163-0090155-00(0), M99-046)
5/26/00	Serial No. 259	2nd Follow up (00P-056-0089342-00(2), M99-046)
5/26/00	Serial No. 258	2nd Follow up (00P-163-0087658-00(2), M99-046)
5/23/00	Serial No. 257	Initial Report (00P-163-0089963-03(0), M99-046)
5/23/00	Serial No. 256	Initial Report (00P-062-0089902-00(0), M99-046)
5/23/00	Serial No. 255	First Follow-up (00P-056-0089644-00(1), M99-046)
5/23/00	Serial No. 254	**Draft Protocol** (M00-154, Ped EAP)
5/23/00	Serial No. 253	**Change in Protocol** (M97-765, #6)
5/19/00	Serial No. 252	Initial Safety Report (00P-028-0089681, M99-046)
5/19/00	Serial No. 251	Initial Safety Report (00P-163-0089904, M99-046)
5/17/00	Serial No. 250	First Follow up(00P-163-0089477-00, M99-046)
5/16/00	Serial No. 249	First Follow up (00P-062-0089624-00, M99-046)
5/16/00	Serial No. 248	Initial Report(00P-056-0089847-00, M99-046)
5/15/00	Serial No. 247	Initial Rerport (00P-163-0089677-00, M98-863)
5/15/00	Serial No. 246	Fifth Follow Up (00P-056-0087187-00, M99-046)
5/12/00	Serial No. 245	First follow up (00P-163-0089392, M99-046)
5/12/00	Serial No. 244	Second follow up ((54008M) 00P-163-0004835, M98-863)
5/10/00	Serial No. 243	Initial report (00P-056-0089644-00, M99-046)
5/10/00	Serial No. 242	Initial report (00P-163-0089643-00, M99-046)

5/10/00	Serial No. 241	Corrected report (00P-163-0089290-00, M98-863)
5/9/00	Serial No. 240	Initial Report (00P-143-0089575-00, M98-863)
5/9/00	Serial No. 239	Initial report (00P-062-0089624-00, M99-046)
5/9/00	Serial No. 238	First follow up (00P-056-0089342, M99-046)
5/9/00	Serial No. 237	First follow up (00P-163-0089122, M99-046)
5/5/00	Serial No. 236	First follow up (00P-163-0088928, M99-046)
5/3/00	Serial No. 235	New Investigator
5/3/00	Serial No. 234	Initial Written (00P-163-0089477-00, M99-046)
5/1/00	Serial No. 233	Initial Written (00P-163-0089290-00, M98-863)
5/1/00	Serial No. 232	Initial Written (00P-163-0089392-00, M99-046)
4/28/00	Serial No. 231	Genl Correspondence (M99-073 elect. data)
4/26/00	Serial No. 230	Initial Written (00P-056-0089342-00, M99-046)
4/24/00	Serial No. 229	Initial Written (00P-143-0088466-00, M98-888, 7 day contact sent 4/17/00)
4/21/00	Serial No. 228	Initial Written (00P-056-0089245-00(0), M99-046)
4/21/00	Serial No. 227	Initial Written (00P-143-0089087-01(0), M98-940)
4/21/00	Serial No. 226	Initial Written (00P-163-0089122-03(0), M99-046, 7 day sent 4/17/00)
4/21/00	Serial No. 225	First Follow-up (00P-163-0087658-00(1), M99-046)
4/18/00	Serial No. 224	Initial Written (00P-163-0088928-00, M99-046, 7 day sent 4/11/00)
4/18/00	Serial No. 223	Fourth Follow Up (00P-056-0087187-00, M99-046)
4/18/00	Serial No. 222	Second Follow Up (99P-184-0008025-01, M98-957)
4/18/00	Serial No. 221	Second Follow Up (99P-184-0008024-00,M98-957)

4/18/00	Serial No. 220	**Protocol Amendments** (M97-720 #7; M98-863 #2; M98-888 #2; M99-046 #3)
4/14/00	Serial No. 219	Initial (00P-163-0088826-00, M99-046)
4/11/00	Serial No. 218	Third Follow Up (00P-056-0087187-00, M99-046)
4/11/00	Serial No. 217	First Follow Up (00P-163-0088319-00, M99-046)
4/11/00	Serial No. 216	Second Follow Up (00P-163-0087323-00, M99-046)
4/5/00	Serial No. 215	**Protocol Amendment No. 1** (M98-957)
4/4/00	Serial No. 214	First Follow Up (00P-163-0087323-00, M99-046)
4/4/00	Serial No. 213	Fourth Follow Up (00P-056-0087030-00, M99-046)
4/4/00	Serial No. 212	Second Follow Up (00P-163-0087485-01, M99-046)
4/3/00	Serial No. 211	Second Follow Up (00P-056-0087187-00,M99-046)
3/29/00	Serial No. 210	Third Follow Up (00P-056-0087030-00, M99-046)
3/29/00	Serial No. 209	First Follow Up (00P-062-0087397-00, M99-046)
3/27/00	Serial No. 208	Initial Report (00P-163-0088319-00, M99-046)
3/21/00	Serial No. 207	Gen'l Correspondence (Patient 321 from 765)
3/21/00	Serial No. 206	**New Investigators**
3/16/00	Serial No. 205	Correspondence (Bio Rqts for ritonavir)
3/16/00	Serial No. 204	First Follow Up (00P-163-0087485-01, M99-046)
3/16/00	Serial No. 203	First Follow Up (00P-056-0087187-00, M99-046)
3/14/00	Serial No. 202	Initial Report (00P-062-0087397-00, M99-046)
3/14/00	Serial No. 201	Second Follow Up (00P-056-0087030-00(2), M99-046)
3/14/00	Serial No. 200	First Follow Up (99P-184-0008024, M98-957)
3/14/00	Serial No. 199	First Follow Up (99P-184-0008025-01, M98957)

3/14/00	Serial No. 198	Initial Report (00P-163-0087658-00, M99-046)
3/13/00	Serial No. 197	Initial Report (00P-163-0087664-00, M99-046)
3/13/00	Serial No. 196	First Follow Up (99P-184-0008016-00, 92610M)
3/8/00	Serial No. 195	Request for Brandname Kaletra to OPDRA
03/06/00	Serial No. 194	Initial Safety Report (00P-163-0087485, M99-046)
03/03/00	Serial No. 193	1st Follow up (00P-056-0087030-00)
03/03/00	Serial No. 192	Request for Brandname Aluvia to OPDRA
03/03/00	Serial No. 191	**Protocol Amendment #1** (M99-056)
03/02/00	Serial No. 190	CMC Amendment (1,2 Dichloroethane)
03/02/00	Serial No. 189	Final Report (M97-741)
02/29/00	Serial No. 188	IND Safety Report (M98-957 1st follow up 00P-056-0086577-00)
02/29/00	Serial No. 187	IND Safety Report (M99-046, 00P-163-0087323-000)
02/25/00	Serial No. 186	IND Safety Report (M99-046, 00P-056-0087187-00, 7day phone report made 2/21/00)
2/22/00	Serial No. 185	IND Safety Report (1st follow up, 98P-163-0004462-02)
2/22/00	Serial No. 184	IND safety Report ((00P-056-0087030-00, M99-046)
2/18/00	Serial No. 183	Safety IND Report (correction to 7-day contact, no longer expedited)
02/15/00	Serial No. 182	**New Protocol** (M99-113)
02/11/00	Serial No. 181	**Correspondence** (X-ref letter ACTG 5014)
02/09/00	Serial No. 180	IND Safety Report (correction to 99P-184-0008016-00(0))
02/09/00	Serial No. 179	IND Safety Report (00P-056-0086577-00, M98-957)
02/07/00	Serial No. 178	**Draft Protocol** (M98-957)

02/03/00	Serial No. 177	Pharm/Tox Amendment (carc study proposal)
02/03/00	Serial No. 176	**Protocol Amendment #2** (M99-046)
01/31/00	Serial No. 175	**New Protocol** (M99-056)
01/28/00	Serial No. 174	**New Protocol** (M99-107)
01/25/00	Serial No. 173	**New Investigators**
01/24/00	Serial No. 172	IND Safety Third Follow up(99P-163-0004918-00)
01/10/00	Serial No. 171	Initial Safety Report (99P-144-0085906-00(0))
01/10/00	Serial No. 170	**Annual Report**
01/07/00	Serial No. 169	Correction to Serial # 166
01/06/00	Serial No. 168	**Draft Amendment** to M99-046
01/05/00	Serial No. 167	**Draft Amendment** to M98-863 and M98-888
01/04/00	Serial No. 166	2nd follow up (99P-163-0004918-00, M98-863) (Original # 54075M)
01/04/00	N/A	Telephone IND Safety Report 99P-144-0085906-00(0)
12/21/99	Serial No. 165	Initial Safety Report (99P-184-0008025-01, M98-957)
12/21/99	Serial No. 164	PK data on disk for Phase I/II
12/17/99	Serial No. 163	**New Investigators**
12/14/99	Serial No. 162	Response to fax for CMC mtg
12/13/99	Serial No. 161	Initial Safety (92618M, M98-957)
12/10/99	Serial No. 160	DMR Reports for 378 PhI studies
12/3/99	Serial No. 159	Safety on 53697M-2 (Correct to 2nd follow up)
12/1/99	Serial No. 158	Pre-NDA CMC meeting package
11/22/99	Serial No. 157	**Protocol Amendment** (M98-863 #1)

11/22/99	Serial No. 156	**Protocol Amendment** (M97-720 #6)
11/16/99	Serial No. 155	First Follow up IND Safety Report (M98-863,54075M)
11/15/99	Serial No. 154	**New Investigators**
11/9/99	Serial No. 153	**Protocol Amendment** (M99-073)
11/8/99	Serial No. 152	Aluviran Correspondence
11/2/99	Serial No. 151	Actis Info for M99-046
10/25/99	N/A	Correspondence
10/15/99	Serial No. 150	Initial IND Safety Report (54075M, M98-863)
10/15/99	Serial No. 149	**Change in Protocol** (Amend 5 M97-765)
10/15/99	Serial No. 148	**Change in Protocol** (Amend 1 of M99-046)
10/13/99	Serial No. 147	**New Investigators**
10/8/99	Serial No. 146	IND Safety Report (1st follow up, 54008M, M98-863)
9/24/99	Serial No. 145	Experimental Designs for solubility/crystallization
9/24/99	Serial No. 144	IND Safety Report (Corrected 92473M)
9/22/99	N/A	Electronic Submission Proposal
9/20/99	Serial No. 143	Info Amendment (Bulk CMC update)
9/15/99	Serial No. 142	**New Protocol** (M99-046 Early Access)
9/13/99	Serial No. 141	Draft Protocol (M99-073, bioequiv. study)
9/13/99	Serial No. 140	**New Investigators**
9/7/99	Serial No. 139	New Protocol (M99-085)
8/27/99	Serial No. 138	**IND Safety Report** (92610M, M98-957)
8/18/99	Serial No. 137	**Draft Protocol** (M99-085)
8/18/99	Serial No. 136	**Protocol Amendment** (Study M98-888)

8/16/99	Serial No. 135	**Pre-NDA Meeting Package Update**
8/13/99	Serial No. 134	**New Investigators**
8/13/99	Serial No. 133	**Informational Amendment** (final report M97-724)
8/9/99	Serial No. 132	**Protocol Amendment** (Study M99-072)
8/02/99	Serial No. 131	**Info Amendment** (Fast Track Designation)
7/23/99	Serial No. 130	**Info Amendment** (Tox report 99/124, 9mo tox)
7/22/99	Serial No. 129	**Info Amendment** (formulations CMC Update)
7/21/99	Serial No. 128	**Info Amendment** (Tox report 99/093, impurities)
7/20/99	Serial No. 127	**Initial Safety Report** (54008M, M98-863 (became 99P-163-0004835))
7/16/99	Serial No. 126	**Bioequivalence proposal** (fed/fast 4-way cross)
7/16/99	Serial No. 125	**Initial Safety Report** (92473M, M98-863)
7/13/99	Serial No. 124	**Pre-NDA Meeting Package** (CMC)
7/12/99	Serial No. 123	**New Investigators** (M98-888)
7/12/99	Serial No. 122	**New Investigators** (M98-863)
7/6/99	Serial No. 121	**ACTIS Info for** M98-888
6/23/99	Serial No. 120	**Draft Protocol** M99-056
6/14/99	Serial No. 119	Early Access Program
6/10/99	Serial No. 118	High Dose study synopsis
6/9/99	Serial No. 117	**New Protocol** (M99-057 interactions)
6/2/99	Serial No. 116	Request for proprietary name (Aluvia)
6/1/99	Serial No. 115	**IND Safety Report** (53697M-2 correct to 2nd follow up)
5/25/99	No Serial No.	Synopsis of QD study M99-056 sent by fax

5/24/99	Serial No. 114	**Protocol Amendment** (M97-765 #4)
5/24/99	Serial No. 113	**Actis Info** for M98-863
5/18/99	Serial No. 112	**IND Safety Report** (2nd follow up 53697M-2)
5/13/99	Serial No. 111	**New (final) Protocol** M98-957 (Ph II w/ Efavirenz)
5/13/99	Serial No. 110	**New(final) Protocol** M98-888(Phase III experienced)
4/8/99	Serial No. 109	**Draft Protocol** M98-888
4/5/99	Serial No. 108	Response to Fax on M98-940 and M98-957
3/31/99	Serial No. 107	**Protocol Amendment** (M97-720 #5)
3/24/99	Serial No. 106	**IND Safety Report** (1st follow up 53697M-2)
3/24/99	Serial No. 105	**Draft Amendment** 1 to M98-863
3/23/99	Serial No. 104	**Preliminary Report** on M98-934
3/16/99	Serial No. 103	**IND Safety Report** (M97-765, initial, 53697M-2)
3/16/99	Serial No. 102	**IND Safety Report** (1st follow up 53559)
3/12/99	Serial No. 101	**Draft Preliminary Safety Report** 53697M-2 (fax)
3/4/99	Serial No. 100	**Draft** M98-957
3/1/99	Serial No. 99	Follow up safety
2/22/99	Serial No. 98	**New Protocol** M98-863
1/27/99	Serial No. 97	**IND Safety report** #53816M
1/22/99	Serial No. 96	Annual Report
1/21/99	Serial No. 95	**Info Amendment** (M97-634 final report)
1/20/99	Serial No. 94	CMC Update (bulk drug chemistry)
1/15/99	Serial No. 93	**New Protocol** (M98-934, co-form with separates)
12/30/98	Serial No. 92	**Info Amendment** (Pharm/Tox 3 mo. study of impurities in

		dogs)
12/30/98	Serial No. 91	**Safety Report** (M97-765)
12/29/98	Serial No. 90	**Revised Protocol** (M98-969 amend #1)
12/15/98	Serial No. 89	**Draft Protocol** (M98-863) and Fax Info from 12/11/98
12/8/98	Serial No. 88	**Protocol Amendment** (New Investigators)
11/24/98	Serial No. 87	**New Protocol** (M98-969, OC Interaction study)
11/17/98	Serial No. 86	**Information Amendment** (Pharm/Tox, Seg II Rabbit and Seg I rat)
11/11/98	Serial No. 85	**Information Amendment** (CMC for 14C study)
11/10/98	Serial No. 84	**New Protocol** (M97-723, C14 Study)
10/3098	Serial No. 83	Response to fax re: M98-933
10/26/98	Serial No. 82	**Information Amendment** (Pre-clin; Study reports for 98/307 & 98/375)
10/23/98	Serial No. 81	**Information Amendment** - CMC update for Bulk Drug
10/19/98	Serial No. 80	**Information Amendment** - CMC (premix formulations for M98-933)
10/16/98	Serial No. 79	**Information Amendment** - Clinical (M98-933; 4 formulations with varying cremophor levels)
10/6/98	Serial No. 78	Request for Meeting (EOPII)
10/6/98	Serial No. 77	M97-741 **(Preliminary Report)**
9/23/98	Serial No. 76	**Protocol Amendment:** Change in Protocol M97-765
8-6-98	Serial No. 75 -	**Information Amendment** - Clinical (M97-650 final, M97-806 and M97-724 prelim)
7-16-98	Serial No. 74 -	**Information Amendment** - Clinical (Investigator Brochure)

7-14-98	Serial No. 73 -	**Information Amendment:** Pharmacology/Toxicology (R&D/98/315 maternal rat study), consultant ECG results for R&D/96/445 and R&D/97/600)
6-30-98	Serial No. 72 -	**Protocol Amendment - New Investigators**
6-25-98	Serial No. 71 -	**Information Amendment:** Clinical (M97-765)
6-23-98	Serial No. 70 -	**Change in Protocol** - (Study M97-765)
6-22-98	Serial No. 69 -	**IND Safety Report** - 3rd Follow-up (M97-720 Case No. 53524M)
6-16-98	Serial No. 68 -	**IND Safety Report** - (M97-720)
6-11-98	Serial No. 67 -	**Information Amendment -** Clinical M97-552 final report
6-9-98	Serial No. 66 -	**IND Safety Report** - 2nd Follow-up (M97-720, 53524M)
6-9-98	Serial No. 65 -	**IND Safety Report** (New, M97-720, 53559M)
6-8-98	Serial No. 64 -	**Information Amendment** - Pharm/Tox (R&D/97/734)
5-28-98	Serial No. 63 -	**New Protocol** (M97-765 #1)
5-26-98	Serial No. 62 -	**IND Safety Report - 1st Follow-up** (PCA 53524M)
5-8-98	Serial No. 61 -	**Information Amendment** - Pharm/Tox (Cytochrome p450 - R&D/97/735)
5-7-98	Serial No. 60 -	**General Correspondence** (M97-704 preliminary data)
5-4-98	Serial No. 59 -	**General Correspondence** (M97-720/M98-863)
5-4-98	Serial No. 58-	**IND Safety Report** (M97-720,53524M,original)
4-22-98	Serial No. 57 -	**New Investigators** (M97-720)
4-16-98	Serial No. 56 -	**Information Amendment** - Clinical (Updated CRO information for M97-720)
4-9-98	Serial No. 55 -	**Information Amendment** - Pharm/Tox (R&D/98/188 - Justification for 9 mo. dog study)
4-8-98	Serial No. 54 -	**Draft New Protocol** (M97-765 #1) COMMENT BY 4/23

4-7-98	Serial No. 53 -	**Response to Request for Information** (Re: Annual Report)
3-11-98	Serial No. 52 -	**Information Amendment** - Pharm/Tox (R&D/97/668 - Met & Disp. of 378 w/ 538 in dog and R&D/97/335 - Seg II DART in Rat)
3-10-98	Serial No. 51 -	**Change in Protocol** (M97-720 #3 W/ group II labels)
3-5-98	Serial No. 50 -	**New Investigators** (M97-720 & M97-806)
3-4-98	Serial No. 49 -	**Information Amendment** - CMC (Oleic acid vs. PG combo capsules)
2-27-98	Serial No. 48 -	**Protocol Amendment: New Protocol** (M97-741 #1)
2-25-98	Serial No. 47 -	**Information Amendment** - Pharm/Tox (Request for Executive Council Review of R&D/97/634, submitted with R&D/97/501 and R&D/97/720)
2-13-98	Serial No. 46 -	**New Protocol** (M97-724; 378 separate w/oleic/EtOH to co-form PG)
2-2-98	Serial No. 45 -	**Change in Protocol** (M97-806 #2)
1-30-98	Serial No. 44 -	**Draft Protocol** - (M97-720 #3 w/ m97-806 Safety Data)
1-21-98	Serial No. 43 -	**Information Amendment** - Pharm/Tox (R&D/97/752, R&D/96/487, R&D/96/669, R&D/96/773, R&D/97/079, R&D/97/392, R&D/97/729 & R&D/97/799)
1-16-98	Serial No. 42 -	**Annual Report** (11/1/96 - 10/31/97)
1-15-98	Serial No. 41 -	**Change in Protocol** (M97-806 #1)
1-15-98	Serial No. 40 -	**Draft Protocol** (M97-806 #2)
1-12-98	Serial No. 39 -	**Change in Protocol** (M97-720 #2)
1-7-98	Serial No. 38 -	**New Investigators** (M97-720)
12-24-97	Serial No. 37 -	**New Protocol** (M97-806)
12-23-97	Serial No. 36 -	**Draft Protocol** (M97-741)

12-18-97	Serial No. 35 -	**Draft Protocol** (M97-720 #2)
12-12-97	Serial No. 34 -	**Draft Protocol** (M97-806 - PK of 378/538 in Healthy)
12-11-97	Serial No. 33 -	**Information Amendment** - Pharm/Tox (R&D/97/573 - 6 mo dog tox, R&D/97/608 - Ex vivo protein binding in human plasma & R&D/97/660 - Effect of 378/538 on ECG End-Pts. in Dog))
11/26/97	Serial No. 32 -	**New Investigators** (M97-720)
11/18/97	Serial No. 31 -	**Information Amendment** - Clinical (M97-720 info to ACTIS)
11/17/97	Serial No. 30 -	**New Protocol** (M97-720 #1)
10/22/97	Serial No. 29 -	**Change In Protocol** (M97-704 #2 & #3)
10/21/97	Serial No. 28 -	**Information Amendment** - CMC (Enteric-coated SEC)
10/16/97	Serial No. 27 -	**Information Amendment** - CMC (White SEC)
10/3/97	Serial No. 26 -	**New Protocol** (M97-733 enteric coated)
9/25/97	Serial No. 25 -	**Information Amendment** - Pharm/Tox (R&D/97/392 & R&D/97/474)
9/22/97	Serial No. 24 -	**New Protocol** (M97-704 #1)
9/16/97	Serial No. 23 -	**Draft New Protocol** (M97-720)
9/5/97	Serial No. 22 -	**Draft New Protocol** (M97-704) and 650 Grp III data
8/1/97	Serial No. 21 -	**Change in Protocol** (M97-650 #5 w/ labeling)
7/22/97	Serial No. 20-	**Draft New Protocol** (M97-650 #5)
7/21/97	Serial No. 19-	**Information Amend** - CMC - bulk chemistry
7-1-97	Serial No. 18 -	**Change in Protocol** (M97-650 #4 w/ labeling)
6-20-97	Serial No. 17 -	**Draft New Protocol** (M97-650 #4)
6-13-97	Serial No. 16 -	**Change in Protocol** (M97-650 #3 w/ labeling)

6-5-97	Serial No. 15 -	**Draft Protocol/Information Amendment**- Clinical (M97-650 #3 Update)
5-28-97	Serial No. 14 -	**New Protocol** (M97-634 #1)
5-2-97	Serial No. 13 -	**New Protocol** (M97-650 #1)
4-17-97	Serial No. 12 -	**Draft New Protocol** (M97-650 w/ 552 data)
4-16-97	Serial No. 11 -	**Information Amendment** - CMC (ABT-378/538 combo 300/50 mg/g & 200/100 mg/g for M97-634)
4-3-97	Serial No. 10 -	**Information Amendment** - Pharm/Tox (R&D/96/574 - 3 mo combo in rat)
3-14-97	Serial No. 9 -	**Draft New Protocol** (M97-650 w/ 552 data)
3-10-97	Serial No. 8 -	**Information Amendment** - Pharm/Tox (R&D/96/675 - 3 mo combo in beagle)
3-3-97	Serial No. 7 -	**Information Amendment** - CMC
2-20-97	Serial No. 6 -	**Information Amendment** - Pharm/Tox (R&D/97/079 - CNS in Mouse and Rat)
2-12-97	Serial No. 5 -	**Change in Protocol** (M96-552 #5)
1-21-97	Serial No. 4 -	**Change in Protocol** (M96-552 #4)
12-24-96	Serial No. 3 -	**New Investigators** (M96-552)
11-27-96	Serial No. 2 -	**Change in Protocol**(M96-552 #2)
11-20-96	Serial No. 1 -	**Change in Protocol** (M96-552 #1)
10-18-96	ORIGINAL SUBMISSION M96-552	

ABT-378 Liquid - IND 55,984

7/04/00	Serial No. 019	**New Protocol** (M99-140)
6/14/00	Serial No. 018	**Updated Investigators** (M98-940)
5/23/00	Serial No. 017	Protocol Amendment (M99-940, #3)
5/19/00	Serial No. 016	Draft protocol (M99-140, Ped EAP)
05/05/00	Serial No. 015	First Follow up (00P-143-0089087, M99-940, initial submitted to 51,715, 4/21/00, serial # 227)
01/03/00	Serial No. 014	**Amendment #1** Protocol M98-940
11/17/99	Serial No. 013	**Updated Investigators** (M98-940)
09/13/99	Serial No. 012	**New Investigators** (M98-940)
08/17/99	Serial No. 011	**Annual Report**
08/13/99	Serial No. 010	**New Investiagors** (M98-940)
08/11/99	Serial No. 009	**Final Study Report** M98-853
06/30/99	Serial No. 008	**New Protocol** M98-940
04/14/99	Serial No. 007	**Protocol** M98-990 Amendment #1
04/05/99	Serial No. 006	Response to 3/26 fax questions
03/23/99	Serial No. 005	CMC Amendment
03/12/99	Serial No. 004	**New Protocol** M98-990
03/04/99	Serial No. 003	Draft M98-940
12/23/98	Serial No. 002	Info Amendment (draft protocol)
10/06/98 853)	Serial No. 001	**Information Amendment** (preliminary report
05/14/98	Serial No. 000	**Original Submission** (M98-853)

Lopinavir Capsule- NDA 21-226

Supplement/ Amendment No.	Description	Submission Date	Approval Date	Comments
Original	Original NDA (159 vols)	12/29/99	9/15/00	Preclinical, PK, M97-720 and M97-765 48 week data (Clin & Stat)
Amendment	Micro Data	1/12/00	9/15/00	References from Micro 1 report
Amendment	Electronic Data (2 disks)	2/22/00	9/15/00	Added "week" variable to M97-720 and M97-765 data
Amendment	CMC, Clin, PK/Bio, Preclin	3/31/00	9/15/00	Preclin, PK, 72 week, CMC
Amendment	Corrected Stats tables	4/10/00	9/15/00	Stats tables for M97-720
Amendment	Virology Data	5/17/00	9/15/00	Spreadsheet
Amendment	Phase III clinical	5/31/00	9/15/00	M98-888, M98-863, M98-957 24 week data, ISS, ISE, Benefit Risk, Label
Correspondenc	Virology Data	6/7/00	9/15/00	Spreadsheet with M98-957 data
Correspondenc	DMR for 940 and 957 for PK	6/9/00	9/15/00	Orig. Submitted to Clin section
Correspondenc	ISS and ISE	6/21/00	9/15/00	Desk copies requested
Amendment	Narratives	6/22/00	9/15/00	Response to request
Amendment	**Package Insert**	**6/22/00**	9/15/00	**Response to request**

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Amendment	CMC Stability Update	6/30/00	9/15/00	12 month capsule, 9 month liquid, final reports for rifabutin and rifampin
Genl Corresp	Dissolution Response	7/5/00	9/15/00	Gen'l description of methods, table of clinical lots and formulation
General Correspondence	Pancreatitis Paper	7/7/00	9/15/00	Update on cases in clinical trial
Genl Corresp	Dissolution Response	7/21/00	9/15/00	DLPs used in clinical studies
Amendment	Safety Update	7/27/00	9/15/00	M98-888 efficacy and safety (n=118 to 24 weeks) M98-863, 720, 765, 940, 957 safety (lab values) update
General Correspondence	Response to fax on Micro	7/27/00	9/15/00	Two methods, 957 analyses
Genl corresp	Stats analysis	8/7/00	9/15/00	48 week and 72 week for 720 and 765
Amendment	Narratives	8/2/00	9/15/00	Response to request
Amendment	Dissolution reports	8/30/00	9/15/00	Not in orig March subm.
Amendment	CMC Response	9/7/00	9/15/00	Response to request caps and bulk
Amendment	CMC Response	9/13/00	9/15/00	Response to request for caps & solt.
Correspondence	Labeling and Phase IV	9/14/00	9/15/00	Draft
Amendment	PI/PPI/bottle/carton/Phase IV/CMC Commit	9/15/00	9/15/00	Final versions

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KALETRA Oral Solution- NDA 21-251

Supplement/ Amendment No.	Description	Submission Date	Approval Date	Comments
Amendment	CMC, Clin, PK/Bio, Preclin	3/31/00	9/15/00	Preclin, PK, 72 week, CMC
Amendment	Phase III clinical	5/31/00	9/15/00	M98-940 24 week data
Correspondenc	DMR for 940 and 957 for PK	6/9/00	9/15/00	Orig. Submitted to Clin section
Correspondenc	940 data on disk	6/14/00	9/15/00	Disk not provided with 5/31 subm.
Correspondenc	ISS and ISE	6/21/00	9/15/00	Desk copies requested
Amendment	CMC Stability Update	6/30/00	9/15/00	12 month capsule, 9 month liquid,
Amendment	Safety Update	7/27/00	9/15/00	M98-940 safety (lab values) update
Amendment	940 response	8/7/00	9/15/00	Response to request for Ped study
Amendment	940 response	8/16/00	9/15/00	Ped study data with listings
Amendment	CMC Response	9/13/00	9/15/00	Response to request for caps & solt.
Correspondence	Labeling and Phase IV	9/14/00	9/15/00	Draft
Amendment	PI/PPI/bottle/carton/Phase IV/CMC Commit	9/15/00	9/15/00	Final versions

Updated September 21, 2000

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